MEDICAL LIBRARY

JAN 3 1934

ARCHIVES OF DISEASE IN CHILDHOOD.

EDITED BY

HUGH THURSFIELD, D.M., F.R.C.P., and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
H. A. T. FAIRBANK, D.S.O., M.S., F.R.C.S.
LEONARD FINDLAY, D.SC., M.D.
A. DINGWALL FORDYCE, M.D., F.R.C.P.EDIN.
C. MAX PAGE, D.S.O., M.S., F.R.C.S.
LEONARD G. PARSONS, M.D., F.R.C.P.
G. F. STILL, M.D., F.R.C.P.
EDITOR OF THE *British Medical Journal*.

Vol. 8. DECEMBER, 1933. No. 48.

CONTENTS

PAGE

Anæmia in Childhood.
Part IX. Anæmia and reticulo-endotheliosis. By Robert Gittins, M.D., M.R.C.P., D.T.M. & H. ... 367

Lipiodol in the diagnosis of congenital œsophageal atresia. By C. Fraser Brockington, M.D., D.P.H., and Reginald Lightwood, M.D., M.R.C.P., D.P.H. 397

Double aortic arch. By Charles E. Snelling, M.B., and I. H. Erb, M.B. ... 401

The incidence of sugars in the urine of infants and children. By M. Fikri, B.Sc., M.B., B.Ch., and Mah. A. El-Sayed, M.B., B.Ch. ... 409

Infantile sepsis and its nutritional effects. By A. G. Ogilvie, M.B., B.S., M.R.C.P. 413

A nutritional disease of childhood associated with a maize diet. By Cicely D. Williams, B.M. ... 423

Index for Volume VIII included.

ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House,
Tavistock Square, W.C.1.

Yearly Subscription (6 numbers), 25/- *Single Number*, 4/6

GENERAL ADVISORY BOARD.

H. T. Ashby (Manchester).
W. R. Bristow (London).
Alan Brown (Toronto).
E. Cautley (London).
Glen Davison (Newcastle-on-Tyne).
T. Y. Finlay (Edinburgh).
G. B. Fleming (Glasgow).
Prof. John Fraser (Edinburgh).
Prof. W. E. Gallie (Toronto).
Sir Archibald Garrod, K.C.M.G. (Oxford).
J. F. Gaskell (Cambridge).
G. R. Girdlestone (Oxford).
H. Tyrrell Gray (London).
Robert Hutchison (London).
R. C. Jewesbury (London).
F. S. Langmead (London).
C. P. Lapage (Manchester).
W. L. Maccormac (Balham).
Helen Mayo (N. Adelaide).
T. P. McMurray (Liverpool).
Charles McNeil (Edinburgh).
A. E. Naish (Sheffield).
D. H. Paterson (London).
W. J. Pearson (London).
F. J. Poynton (London).
T. G. Pugh (Carshalton).
F. C. Pybus (Newcastle-on-Tyne).
Sir Humphry Rolleston, Bt. (Cambridge).
J. D. Rolleston (London).
J. C. Spence (Newcastle-on-Tyne).
E. H. M. Stephens (Sydney).
G. Bruton Sweet (Auckland, N.Z.).
C. W. Vining (Leeds).
E. H. Williams (Dunedin).

NOTICE TO SUBSCRIBERS.

Subscriptions are payable to the Financial Manager of the British Medical Association who has charge of all financial matters concerning the ARCHIVES OF DISEASE IN CHILDHOOD. Address: British Medical Association House, Tavistock Square, London, W.C. 1.

NOTICE TO CONTRIBUTORS.

All papers submitted for publication should be sent to Dr. Alan A. Moncrieff, 121, Harley Street, W. 1. All other editorial matters should be referred to Dr. Charles Harris, 31, Weymouth Street, W. 1.

Papers sent for publication should be typewritten. Illustrations will usually be inserted in the text itself, and care should be taken that the text is marked to show the desired position of each illustration.

Charts and curves accompanying papers should be carefully drawn, on tracing linen. Any lettering on these drawings should be lightly inserted in pencil.

Contributors will receive one proof in page, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Contributors will be supplied with reprints of their articles at cost price if application is made when returning proofs. An estimate of costs will be given if desired on application to the Financial Manager of the British Medical Association.

Papers which have been published become the property of the ARCHIVES and permission to republish must be obtained from the Editors.

STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part IX.—Anæmia and reticulo-endotheliosis

BY

ROBERT GITTINS, M.D. M.R.C.P., D.T.M. & H.

In recent years the subjects of both anæmia and the reticulo-endothelial system have separately received much attention; they have offered interesting problems to the clinician and the pathologist, and great advance has been made in our knowledge of the causations of the one and the activities of the other. It is, therefore, somewhat surprising that more attention has not been given to the part played by the reticulo-endothelial system in the various forms of anæmia. To this system has been attributed the role of scavenger of cellular debris, chemical by-products and toxins of various kinds, and also a share, regarded by some as important, in hæmopoiesis. On a priori grounds it would seem probable that the reaction of the reticulo-endothelial system in the various anæmic states would be of some importance, and that its study might throw some light on the nature of the processes at work.

From time to time instances occur in children of both acute and chronic anæmia that do not correspond satisfactorily with hitherto recognized syndromes. Four such cases have recently been observed at the Birmingham Children's Hospital, and it is the object of this paper to record them in some detail with special reference to the changes found in the reticulo-endothelial system. It will be advantageous to anticipate the chief conclusions by stating here that of these four cases, two appeared clinically to be instances of acute erythrocnoclastic (hæmolytic) anæmia, and two have, subsequent to histological investigation, been regarded as examples of the same disease process in a chronic form. In all four cases the elements of the reticulo-endothelial system showed outstanding activity. This, however, differed in form and degree not only in each case, but also from other forms of reticulo-endothelial activity, such as are seen, for example, in Gaucher's disease and other reticulo-endotheliosis. This activity has been regarded as a response to damage to the hæmopoietic apparatus. Further, it is probable that similar findings may be taken as one of the chief forms of evidence of the existence of an erythronoclastic process.

Case 1.—J. W. The clinical features of this case were given in Part V of this series (p. 188), and only a brief summary is given here. This child, aged

21 months, had always been pale, and developed small scattered staphylococcal abscesses, following which the anæmia increased. The spleen and lymphatic glands were slightly enlarged; there was no icteric tinge, but the blood contained ·4 units of bilirubin. The blood examination showed an aplastic picture: Hb. 26 per cent.; red cells 1,360,000 per c.mm., of which only ·2 per cent were reticulocytes; white cells 950, of which only 8 per cent. were granulocytes; platelets 21,300 per c.mm. Although there was a slight improvement in the state of the blood, a temperature of 105° supervened and death occurred.

AUTOPSY. Nutrition fair, considerable pallor. Thymus, normal. Tonsils, normal appearance. Liver, some fatty change and enlargement. Spleen, somewhat enlarged. Lymphatic glands of mesentery, neck and groins not definitely enlarged. Marrow of left femur red throughout, but in one or two areas, there was a suggestion of a ' red currant jelly ' appearance.

HISTOLOGICAL EXAMINATION: tissues placed in neutral formalin 15 hours post mortem in October, and stained with hæmatoxylin and eosin.

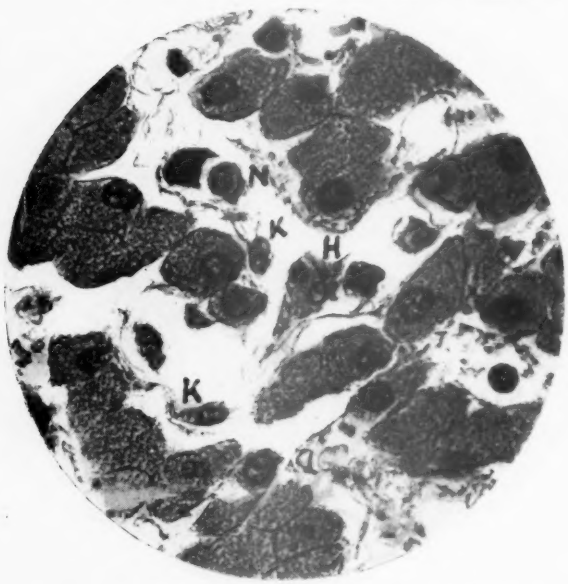


FIG. 1. Case 1.—Liver (× 700). Placed in neutral formalin 15 hours post mortem in October. Stain H.E. A histiocyte (H), which has ingested a nucleus, and an erythrocyte, loosened Küpffer cells (K), and ? normoblasts (N) are seen in widened sinusoids.

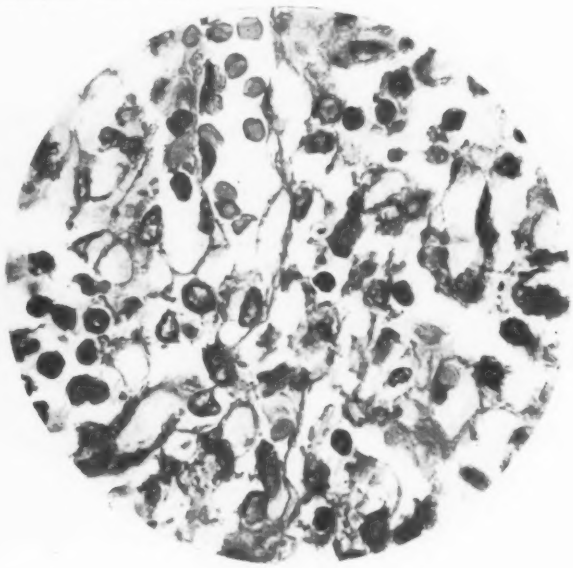


FIG. 2. Case 1.—Lymph gland (× 700). Placed in neutral formalin 15 hours post mortem in October. Stained H.E. The proliferated reticulum and reticulum cells are evident.

Spleen. Lymph follicles small, pulp filled with large pink cells, no fibrosis, no congestion. Under high power (see Fig. 4) there was seen increase of reticulum fibres, which were thicker than normal. Numerous large pale cells were present; the cytoplasmic processes of some appeared to be in close relation with the reticulum, while other similar cells appeared to be lying free. The cytoplasm of these large cells was slightly granular, faintly eosinophilic and variously shaped; the longest diameter of these cells was often between 13 and 18μ. Their nuclei, usually about 8μ in diameter, were oval, bean-shaped, or sometimes bluntly lobulated and bounded by a delicate membrane; they stained rather faintly and the basi-chromatin was distributed in scattered small particles or finely threaded, so that the appearance was often sponge-like; a nucleolus was sometimes discernible. The free cells frequently contained one or more ingested red cells. Their characters, therefore, were those of histiocytes, and owing to the close similarity of their features with those of the swollen reticulum cells, it appeared that the free and fixed cells were of the

same type and that the histiocytes were being produced from the reticulum cells. The cells lining the venous sinuses were not much enlarged nor phagocytic. Most of the remaining free cells were lymphocytes and a few myelocytes. In the centres of the follicles a few large pale cells were present. The Turnbull-Huecke preparation showed considerable quantities of hæmosiderin, which was chiefly contained in reticulum cells and histiocytes. Bielchowsky's silver stain revealed a slight increase in the condensed reticulum fibres. The striking feature was the large number of free phagocytic histiocytes.

Liver. There was œdema and the liver cell columns were broken up by wide sinusoids which contained irregularly shaped large cells. Under higher magnification (Fig. 1), in the sinusoids there was much amorphous eosinophilic material and many histiocytes, some of which were phagocytic. Many Küpffer cells, which were still lying against the wall of the sinusoids, were swollen and partially free; their nuclear characteristics closely resembled those of the histiocytes. Turnbull-Huecke preparations showed slight hæmosiderin deposit mainly in the Küpffer cells and histiocytes.

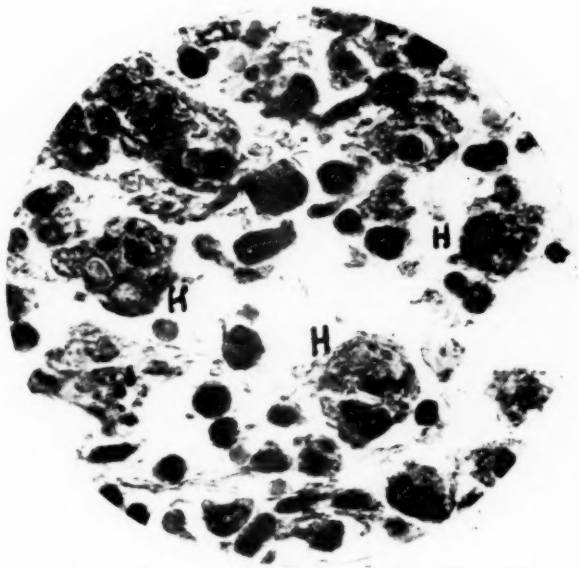


FIG. 3. Case 1.—Marrow (× 700). Placed in neutral formalin 15 hours post mortem in October. Three large histiocytes (H) containing several ingested red cells in the small area of this oil immersion field.

Lymph gland. There was widespread increase of reticulum tissue, in which the remains of follicles were discernible with difficulty; the germ centres were large. The characters of the reticulum and the reticulum cells were as described in the spleen. Lymphocytes were reduced. There was slight fibrosis of the capsule and around the vessels, all of which were congested. Some of the lymph sinuses stood out as columns of pink cells. Under the high power (Fig. 2) the germ centres consisted of cells with characters similar to the reticulum cells; their processes were branched to a certain degree. Free histiocytes were fairly numerous. There were also swelling, proliferation and liberation of the endothelial cells lining the lymph sinuses, which contained some histiocytes. By the Turnbull-Huecke method a fair proportion of histiocytes showed iron. The picture was that of considerable proliferation of reticulum, sinus endothelial and germ centre cells, together with an increase of histiocytes at the expense of the lymphatic tissue.

Bone marrow. Cellular; many of the cells appeared large and irregular, and the relatively regular shapes of the cells of normal marrow were missing. Under the high power (Fig. 3) the large cells were seen to be histiocytes, showing a remarkable

degree of phagocytosis of erythrocytes; some of them contained as many as 7 red cells, packed closely together in their cytoplasm. One histiocyte measured 23μ and contained 2 polymorphonuclear cells and several red cells. Myelocytes, meta-myelocytes, and polymorphonuclear cells were present but fewer in number than normal; some of the cells with nuclear polymorphism were somewhat large for granulocytes since they measured 10 or 11μ, and their characters were rather histiocytic. Normoblasts were fairly plentiful. A slight hæmosiderin deposit was demonstrated in the Turnbull-Huecke preparation. The striking feature was the large number of intensely phagocytic histiocytes, though the fixed reticulum was not proliferated.

Kidney. Cloudy swelling of tubule cells and œdema.

Tonsils. A good deal of proliferation of reticular cells of the germ centres, but not much in the pulp.

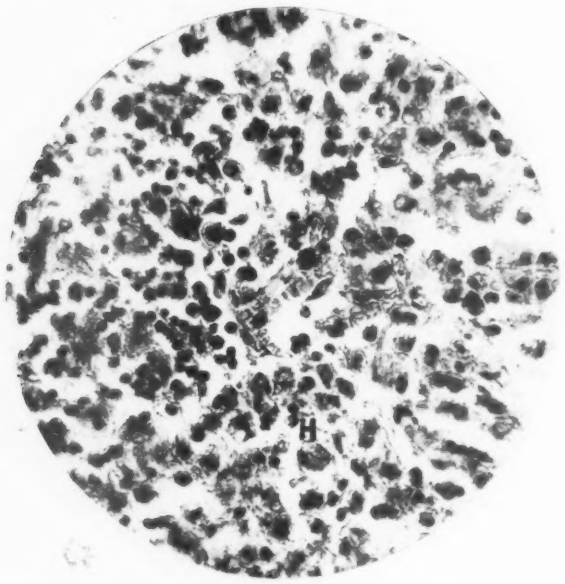


FIG. 4. Case 1.—Spleen (× 360). Placed in neutral formalin 15 hours post mortem in October. Stain H.E. Increase of reticulum cells is present, a phagocytic histiocyte (H) lies towards the bottom of the field.

Lungs. Some bronchial catarrh; much patchy collapse and compensatory emphysema; congestion. Polymorphonuclear granulocytes and histiocytes present in capillaries.

Summary.—A case of subacute erythronoclastic anæmia of aplastic type, showing on histological examination great activity of the reticulo-endothelial system, especially in the production of numerous phagocytic histiocytes.

Case 2.—B. M. Fuller clinical and hæmatological details of the first part of the illness in this case were given in Part IV of this series (p. 166).

The patient, a female child, who was aged 17 weeks on admission, had been pale at birth and slightly jaundiced a fortnight later. She had been fed on the breast for seven weeks and afterwards on Ostermilk.

On admission, nutrition was good, severe anæmia with slight jaundice was present and the spleen was greatly, and the liver moderately, enlarged; a few shotty glands were found in the axillæ. A blood examination showed: red blood cells 1,450,000

per c.mm., hæmoglobin 21 per cent., colour index ·72; the volume index was ·86, and the saturation index ·87; there were anisocytosis, poikilocytosis and polychromasia; the fragility of the red cells was slightly increased; a Price-Jones curve showed much anisocytosis and a mean diameter of 6·794μ; the white blood cells were 18,700 per c.mm. of which 63·5 per cent. were lymphocytes, 3 per cent. myelocytes, ·5 per cent. myeloblasts and 11 per cent. monocytes; platelets were reduced; 1·5 normoblasts and 9·5 macro-normoblasts per 100 leucocytes were found (six days after transfusion of two ounces of blood). Urobilin was present in the urine and 1·0 units bilirubin were present in the blood. The Wassermann reactions of the patient and her parents were negative.

The child remained in hospital until her death nearly 4 months later. During this time eleven blood transfusions were given; in addition, ferrous sulphate (gr. 2 t.d.s) in the early stages, and campolon (liver extract) injections towards the end, were administered. From time to time some petechiæ and ecchymoses were seen. The spleen became smaller, though fluctuations in size were noted. The general condition and the state of the blood improved after two blood transfusions, to be followed by a definite fall in the hæmoglobin and red cell content; after further blood transfusions improvement was maintained until about one week before death. Hæmoglobin rose to 66 per cent. at its highest point; the colour index was always high after the first examination, sometimes over unity; the volume and the hæmoglobin saturation indices of the red cells remained approximately at unity. The bleeding time was found to be prolonged and the clot retraction was poor; the clotting time was approximately normal. Although signs of regeneration were pronounced in the early stages, when there were also leucocytosis and some immaturity of the granulocytes, at the later blood examinations only ·6 per cent. reticulocytes were present, anisocytosis and poikilocytosis were very much less than previously and a Price-Jones curve revealed a mean diameter of only 6·393μ. The monocytes varied in number but were usually slightly increased. A blood examination about one week before death showed that the white cells numbered only 9,500 per c.mm., and although the lymphocytes still accounted for 54·5 per cent., the immaturity of the granular series was much less.

Radiograms of the long bones showed some rarefaction and thinning of the cortex.

Autopsy. Development poor, nutrition fair, considerable pallor and a slight yellowish tinge. Pericardium contained a little yellowish fluid. Epicardium showed a few petechiæ. Liver, rather pale, with early fatty change. Spleen, dark and enlarged to approximately four times normal size. Mesenteric and inguinal glands slightly enlarged. Frontal bones showed raised red areas (Fig. 18) and the left femur externally appeared dark red at both ends; on section the marrow was rich red in colour.

There were small extravasations of blood beneath the vertex of the skull and in the orbits.

Histological examination: tissues placed in neutral formalin nine hours post mortem in May.

Spleen. Lymph follicles small, composed of small dark and large pale cells. Reticulum cells in pulp prominent. High power:—'Germ centre' cells and reticulum in follicles proliferated. The small dark cells noted under the low power were lymphocytes, normoblasts and normoblastic nuclei. In the pulp the reticulum cells were enlarged and proliferated, and the appearance was similar to that in the first case, except that free histiocytes were few and phagocytosis was slight. The Turnbull-Huecke preparation showed a little scattered hæmosiderin. Silver stain did not reveal any gross increase in reticulum fibres.

Liver. Portal tracts normal. Many small cells scattered in sinusoids. High power (Fig. 5):—Liver cells contained some bile pigment. Most cells in sinusoids were erythroblasts: normoblasts with a few megaloblasts and pro-erythroblasts.

Histiocytes, containing erythroblastic nuclear fragments, bile pigment, etc., were fairly numerous. Küpffer cells were swollen and scarcely any normal forms were found. An extremely heavy deposit of hæmosiderin, chiefly in the peripheral areas of the lobules, was demonstrated by the Turnbull-Huecke method.

Lymph gland. Features similar to those described in the spleen. Free phagocytic histiocytes were present. Lymph sinuses were very wide and contained many histiocytes. The Turnbull-Huecke method showed a slight scattered deposit.

Bone marrow. Many normoblasts and pro-erythroblasts in all regions. Phagocytic histiocytes numerous.

Summary.—A case clinically resembling so-called von Jaksch's anæmia in an infant aged 4 months; histological examination showed considerable abnormal erythropoiesis and widespread reticulo-endothelial activity.

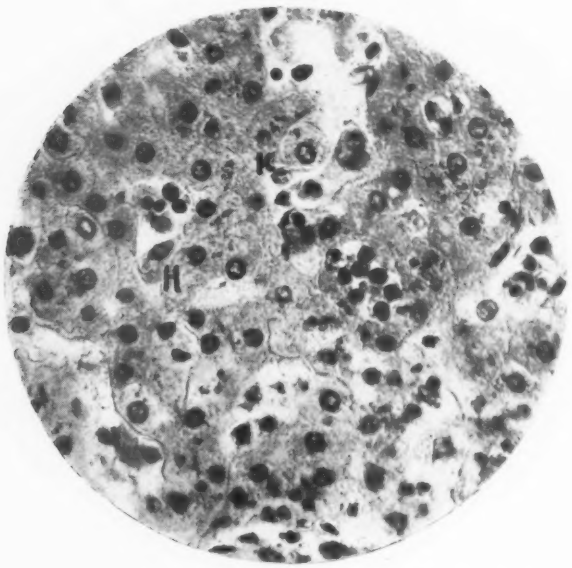


FIG. 5. Case 2.—Liver (× 420). Placed in neutral formalin 10 hours post mortem in May. Stain H.E. Shows erythropoietic foci, histiocytes (H) and swollen Küpffer cells in sinusoids.

Case 3.—J. B., male, 1 year old, one of twins, had been breast fed for 3 months. He had always been somewhat pale, but 1 week before admission the pallor had rapidly increased. Examination revealed considerable anæmia, purpura, rickets, the liver enlarged nearly to the umbilicus, considerable enlargement of the spleen, and a few enlarged lymph glands. The respiration rate after admission was 60 and over, and 4 days after admission signs of broncho-pneumonia were evident. Blood examination: Hæmoglobin 34 per cent., red blood cells 3,300,000, white blood cells 34,200 per c.mm., colour index 0·52, size of red cells (Eve's halometer) 7·23μ. A differential count showed slight immaturity of the granular series with eosinopenia; the actual percentages were as follows: neutrophil polymorphonuclear cells, segmented, 40; neutrophil polymorphonuclear cells non-segmented 18; neutrophil metamyelocytes mature, 2; neutrophil metamyelocytes immature, 1; neutrophil myelocytes, ·5; lymphocytes, 27·5; plasma cells, ·5; monocytes, 10·5. There were 700 normoblasts, 350 macronormoblasts and 350 megaloblasts per c.mm. Poikilocytosis and anisocytosis were well marked, and there was some polychromasia. The platelets

appeared normal in the film. The radiogram of forearm showed florid rickets. The child's condition deteriorated and death took place 4 days after admission—11 days from the onset of acute illness.

Clinically it appeared that an acute respiratory infection had overwhelmed the child, who was already suffering from a chronic erythronoclastic anæmia and nutritional deficiency.

Autopsy. Bilateral empyemata and massive consolidation in lungs with some grey hepatization. Liver enlarged (410 grm.) showing some toxic pallor and early fatty change. Spleen grossly enlarged, slightly hard, and of a more or less normal colour. Inguinal lymph glands only were very slightly enlarged and congested. Bone marrow of femur a greyish-red colour. Costochondral junctions showed well marked rickets.

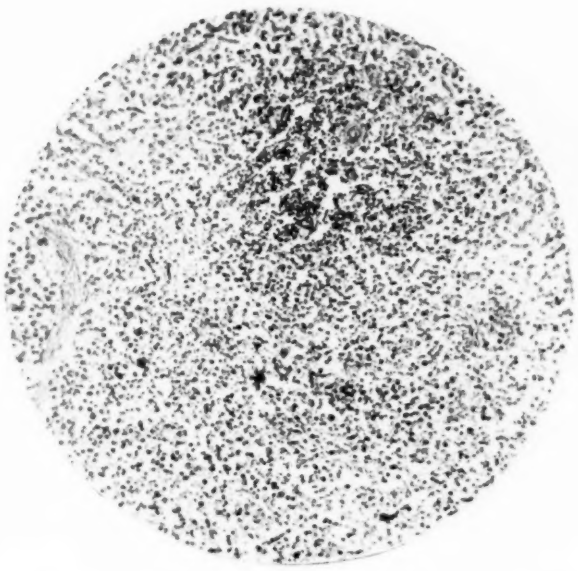


Fig. 6. Case 3.—Spleen (× 75). Placed in formalin 17 hours post mortem in August. Stain H.E. Apart from the lymphoid follicle in upper part, the tissue shows widespread increase of reticulum, enclosing but few lymphatic cells. No myeloid metaplasia.

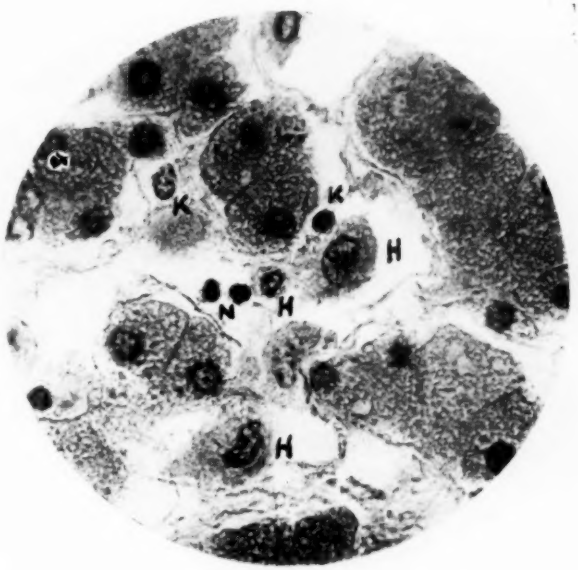


Fig. 7. Case 3.—Liver (× 700). Placed in formalin 17 hours post mortem in August. Stain H.E. Histiocytes (H), loosened Küpffer cell (K), normoblasts (N), are seen in wide sinusoids.

Histological examination: tissues placed in formalin about 24 hours post mortem in August.

Spleen (stained with H.E.). Under the low power (Fig. 6), there was considerable increase of the pulp and the follicles were diminished; fibrous tissue was not obviously increased. Under the high power many of the cells were histiocytes and swollen fixed reticulum cells, as described in Case 1; the nuclei were often irregularly lobed and a few showed one or two nucleoli. The free histiocytes were fewer than in Case 1, and although there was some phagocytosis it also was very much less. Myelocytes, some of which showed granulation, and polymorphonuclear cells were found scattered in the reticulum. The outstanding feature was the increase in reticulum cells and fibres, which was well shown by Bielchowsky's silver impregnation method. Much scattered hæmosiderin was found by the Turnbull-Huecke method.

Liver. The cell columns were broken up by œdema; there were some central fatty change and a slight increase of small round cells along the portal tracts. Under the high power (Fig. 7, 8 and 9) the widened sinusoids contained various cells, some of which appeared to be polymorphonuclear granulocytes and myelocytes, while the remainder were histiocytes, which had frequently ingested either lymphocytes or polymorphonuclear cells. No entirely normal Küpffer cells were found. One of several preparations by the Turnbull-Huecke method showed a very light irregular deposit of hæmosiderin.

Lymph glands. Sections from several glands were examined, all of which showed congestion and œdema so that the cells were rather widely separated. One gland, probably from the hilum of the lung, showed much catarrh of the sinus endothelium,

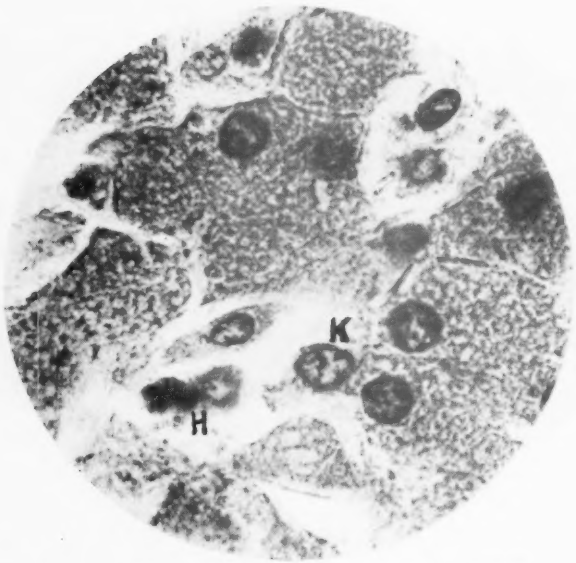


FIG. 8. Case 3.—Liver (× 900). Stain H.E. Shows phagocytosed nucleus in histiocyte (H). (K) is probably a swollen Küpffer cell.

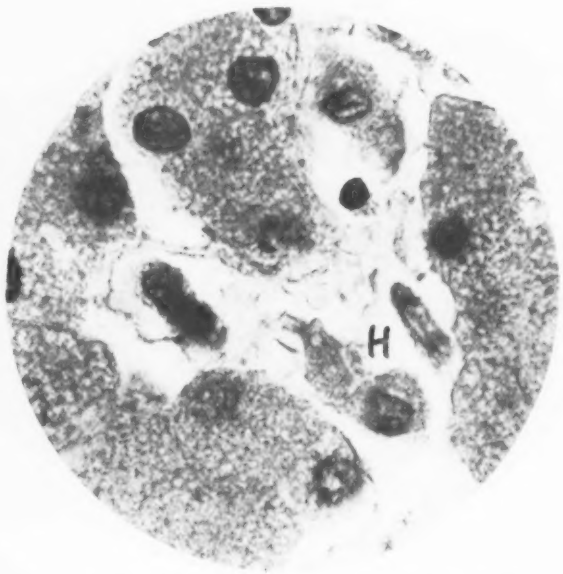


FIG. 9. Case 3.—Liver (× 900). Stain H.E.

and many large pink cells were massed together in the sinuses. Under the high power (Fig. 10) these large free cells were often foamy in appearance, and displayed much phagocytosis. In only one section was there seen to be a slight swelling of the reticulum cells.

Bone marrow. Cellular, with small fat spaces. Under the high power (Fig. 11) most of the cells appeared to be either normoblasts, megaloblasts or pro-erythroblasts; myeloblasts and myelocytes were present in only moderate numbers. Mature granulocytes were diminished, and few reticular cells were distinguished.

Lung. There were much congestion and many small areas of collapse and compensatory emphysema. Many of the alveoli contained free mononuclear cells. The section was evidently not taken from a densely consolidated area.

Heart. The fibres were small and separated by œdema; many were broken and granular.

Kidneys. Slight catarrhal and toxic changes in the tubule cells.

Summary.—A case of chronic erythronoclastic anæmia of milder type associated with nutritional deficiency; in which pneumonia supervened and brought about a fatal termination. Histologically reticulo-endothelial activity appeared to be more limited than in the other cases, and was confined mainly to the splenic reticulum and liver sinusoids.

Case 4.—R. D., male, aged 1 year and 11 months when first seen. He was in hospital several times and many investigations were carried out before his death at an age of 3 years, 9 months. He was an only child, born at full term and weighing eight pounds. When first admitted on the 15th April, 1930, it was learned that he had been yellow at birth, but the jaundice soon cleared; he had always been pale. At the age of 15 months he bled profusely after circumcision; he had always bruised easily and some time before admission he had shown some melæna. His maternal grandfather was said to be a bleeder.

Clinical examination revealed extreme pallor and a slight icteric tinge, but no other abnormal signs, except a spleen enlarged by three inches. The blood examination showed hæmoglobin 37 per cent., red blood cells 2,500,000 and white

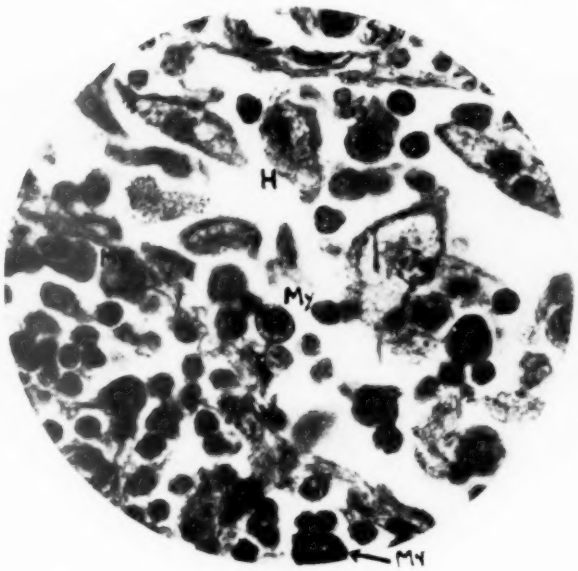


FIG. 10. Case 3.—Lymph gland and sinus (× 700). Placed in formalin 17 hours post mortem in August. Stain H.E. Numerous histiocytes are prominent. Cell H shows ingested red cell. A few myelocytes (My) were present.

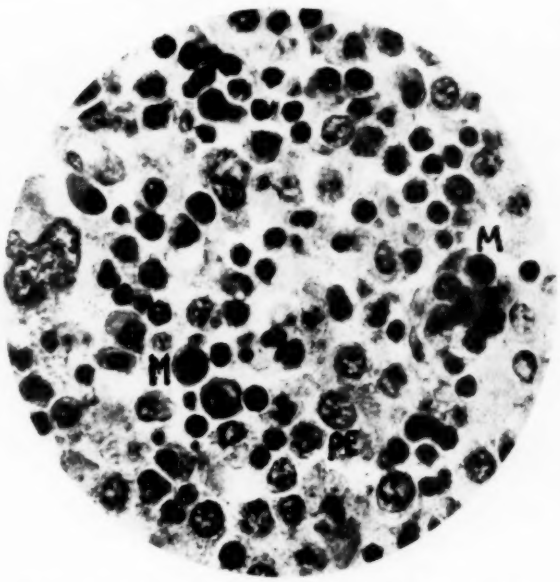


FIG. 11. Case 3.—Marrow (× 700). Stain H.E. Shows a considerable number of normoblasts. Cells PE, myeloblasts or pro-erythroblasts. Although pneumonia and empyema were present, erythropoiesis is much in excess of granulopoiesis: no definite myelocytes, metamyelocytes or polymorpho-nuclears are present (M) cell of megaloblast type.

blood cells 11,300 per c.mm. The percentage differential count showed neutrophil polymorphonuclear cells, 44; neutrophil myelocytes 2; eosinophil polymorphonuclear cells 1; lymphocytes 53; and a few normoblasts were present. There was slight increase of urobilin in the urine, the Wassermann reaction was negative and the fragility of the red cells was slightly increased (incomplete hæmolysis in 0·5 per cent. saline, while the control showed it in 0·45 per cent.). Treatment comprised the administration of iron and copper, fresh lettuce, and a transfusion of 200 c.cm. of blood. The child was discharged after 7 weeks improved, with a hæmoglobin content of 40 per cent.

The child was re-admitted into hospital four times in the next twenty months, for fairly lengthy periods, and although at times he seemed slightly better, his condition slowly and insidiously deteriorated. Bleeding, especially from the nose and stomach, became more frequent and copious, and petechiæ and ecchymoses were often observed; there was a gradual increase in the size of the spleen and liver, but glandular enlargement was never noticeable. Occasional slight rises in temperature

occurred with increasing frequency. The slight increase in the fragility was again found, and the van den Bergh test gave very slight positive direct and indirect reactions. In all, thirty-six blood counts were carried out, but none showed any important changes from the first; the reticulocyte response was usually low, but sometimes rose to 3 and even on one occasion to 6 per cent. The hæmoglobin rose to 40 per cent. 3 weeks after the first estimation, but subsequently there was a fall with minor fluctuations to less than 15 per cent.; the colour index, never high, tended to decrease; nucleated red cells were found only occasionally; the platelets decreased ultimately to 10,000 per c.mm.; the white cells diminished to 4,000 per c.mm., and differentially the lymphocytes usually amounted to 50 per cent., one or two myelocytes and metamyelocytes were present, the monocytes were not increased, and the basophil cells disappeared.

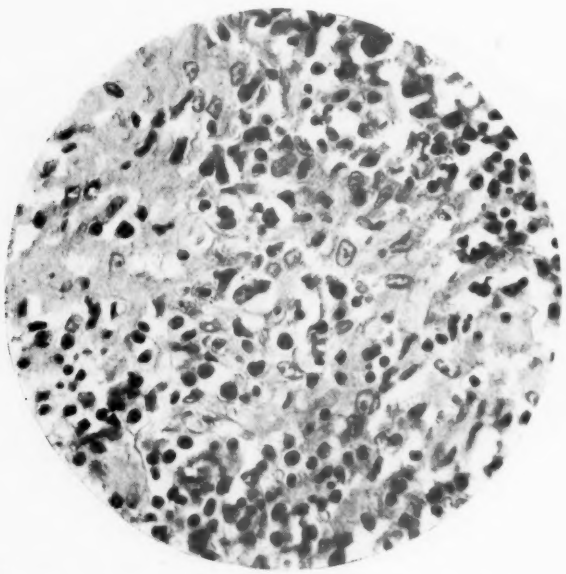


FIG. 12. Case 4.—Spleen (× 360). Tissues placed in neutral formalin 3 hours post mortem in February. Stain H.E. Shows gross proliferation of reticulum cells and increase of reticulum fibres.

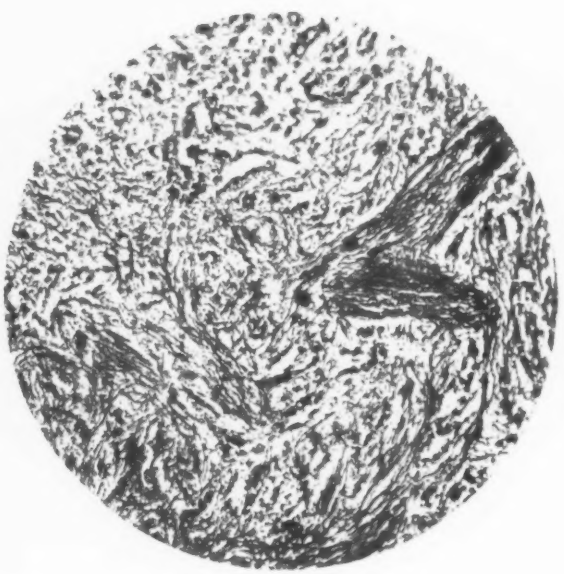


FIG. 13. Case 4.—Spleen (× 95). Bielchowsky's silver stain, frozen section. Great increase and thickening of reticular fibres.

A wide range of therapeutic agents used at various stages included a course of injections of healthy adult blood serum, X-ray applications to the bones and later to the spleen, dried yeast, vitamin D, histidine, suprarenal cortex (opocap) by mouth, adrenalin injections, when the bleeding was troublesome, and, of course, frequent blood transfusions. Nothing, however, appeared to have any definite effect on the course of the illness or the state of the blood. Towards the end efforts were chiefly directed towards staying the frequency and the amount of the hæmorrhages; and finally the child died after further hæmatemesis and epistaxis.

As the illness progressed it was obvious that we were dealing with a most unusual form of anæmia; the failure of normoblasts to appear in any number and the relative maturity of the granulocytes did not lend support to a diagnosis of von Jaksch's anæmia. A diagnosis of splenic anæmia, of adult type, had some features in its favour; the age of the child at the onset was, however, against its being the correct diagnosis. A storage reticulo-endotheliosis such as Gaucher's disease, had to be considered, but was ruled out because of the progressive and severe character of the anæmia and lack of familial incidence. A diagnosis of aplastic anæmia, which may be a phase of erythronoclastic anæmia, accorded with the unusual blood picture and

was supported by the histological findings, which included the replacement of large portions of the marrow by reticular proliferation.

HISTOLOGICAL EXAMINATION: sections placed in neutral formalin or Zenker's solution 3 hours post mortem in February.

Spleen. Under the low power lymphocytes in follicles much diminished, but in the centre of thin rings of lymphocytes, were extensive closely packed collections of large pale cells; considerable increase in pulp, which appeared to consist mainly of of rather large pale cells, increased reticulum and a fair number of red cells; some perivascular fibrosis; in places the fine reticulum fibres were conglomerated into bundles or strands, which showed little structure and sometimes hyaline change; in others were strands of apparently fine fibrous tissue. Under high magnification (Fig. 12) the numerous and prominent reticulum cells were swollen and

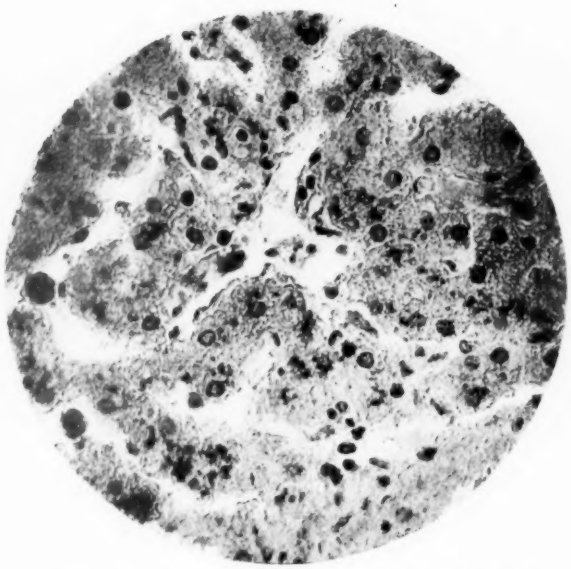


FIG. 14. Case 5.—Liver (× 420). Turnbull-Huecke preparation showing small granules of hæmosiderin in liver cells. Sinusoids are wide and contain swollen Küpffer cells and histiocytes.

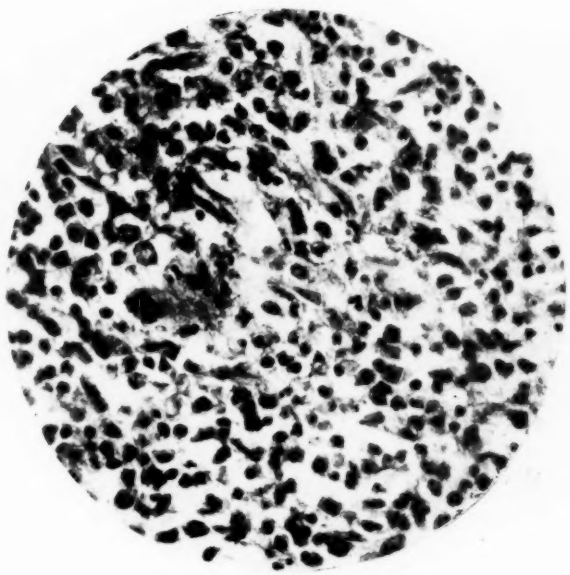


FIG. 15. Case 5.—Bone marrow of femur (× 360). Proliferation of reticulum cells and fibres seen in one of the more normal portions.

contained large pale nuclei; their characters were similar to those described in the previous cases. Free histiocytes and cells with definite ingested matter were not found. The venous sinuses were not generally dilated, but their characteristic lining cells (with fairly large slightly irregular nuclei and little cytoplasm) were somewhat prominent and easily distinguished, and were sometimes lying free in the lumina. In some areas the bundles of reticular tissue appeared to show partial necrosis. One section showed fairly numerous large dark cells, 10 to 11μ in diameter, with nuclei 8μ which contained rather large irregular masses of chromatin and one or two dark nucleoli; these cells resembled myelocytes, but were rather irregular in shape. The Turnbull-Huecke process revealed a slightly increased deposit of hæmosiderin, irregularly scattered in the reticulum, and the silver stain showed gross increase in reticulum fibres (Fig. 13). The striking features were the great increase of reticulum fibres and large pale nuclei, the presence of small bundles and strands of reticulum fibres, and the occurrence of syncytial groups of pale cells.

Liver. Much fatty degeneration in the central areas of the lobules; slight periportal infiltration of lymphocytes and fibroblasts; many nuclei and cells of all shapes in the

widened sinusoids. Under high power liver cells contained groups of light yellow-brown granules. There were many free histiocytes in the sinusoids; their nuclei were often horseshoe-shaped, some were phagocytic and vacuolated. Other cells in the sinusoids were lymphocytes in moderate numbers and a few small (?) myelocytes. No absolutely normal Küpffer cells were found; those that were attached to the walls of the sinusoids were slightly swollen and possessed nuclei slightly darker than, but similar in texture and shape to, those of the histiocytes. The Turnbull-Huecke method showed some deposit of hæmosiderin in the liver cells (Fig. 14).

Lymph glands. Lymph follicles were much diminished and often difficult to discover and identify. There was a striking increase of reticulum and reticulum cells throughout and lymphocytes were sparse, but the endothelial cells

FIG. 16. Case 4.—Bone marrow of femur (× 95). This section shows how the hæmopoietic tissue was replaced by bundles and strands of reticular fibres; this is a later stage of the process seen in Fig. 15.

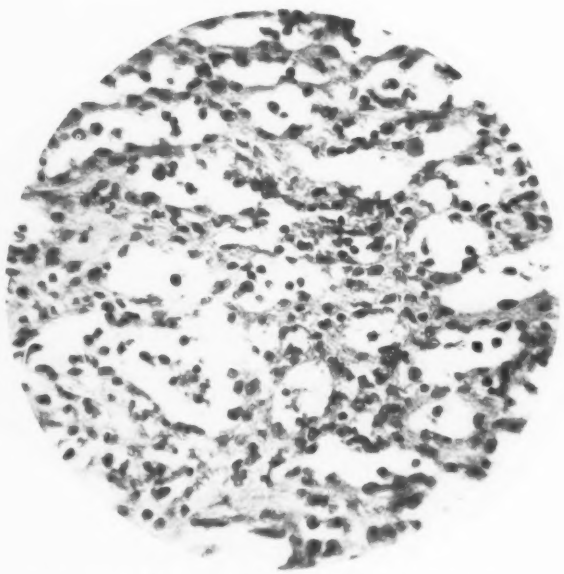


FIG. 17.—Splenic anæmia of adult type in a child aged 7 years. Spleen (× 230). Stain H.E. The cirrhosis between the dilated venous sinuses is well shown and is different from the reticulum cell proliferation shown in Fig. 12.

of the lymph sinuses were not proliferated nor prominent, nor were these sinuses packed with cells. Under the high power the proliferated reticulum cells appeared similar to those described in the other cases and possessed the same characteristic pale sponge-like nuclei; their cytoplasm was moderately eosinophilic, and on the whole their processes were bluntly contoured. In the meshes the free cells consisted of some lymphocytes, a few myelocytes and, in contrast to the spleen, some free histiocytes, which sometimes contained a rather foamy cytoplasm, vacuoles and a few ingested particles. The Turnbull-Huecke process showed some doubtful irregular deposits of hæmosiderin. A gland from the meso-colon appeared more normal as regards the reticulum, but the lymph sinuses were dilated and packed with apparently normal lymphocytes and histiocytes.

Bone marrow. The sections from different portions of the marrow showed some differences: thus in some there was an increase of pale reticulum cells (Fig. 15), whereas in others there were numerous scattered bundles of fine reticular fibres, fibrous tissue or almost structureless eosinophilic material (Fig. 16). Under the high power the other cells were identified as some eosinophil leucocytes, and scattered mature red cells and normoblasts, which tended to be aggregated into small

foci of erythropoiesis. Pro-erythroblasts were not numerous, and hæmopoietic areas were severely diminished.

Kidney. All tubules showed advanced cellular degeneration and were dilated; there were no infiltrations and no increase in interstitial cells; the glomerular tufts were rather large.

Lungs. The bronchi contained masses of leucocytes; there were small areas of collapse and emphysema; some capillaries contained some large pigment carrying cells, 10 to 11μ in diameter.

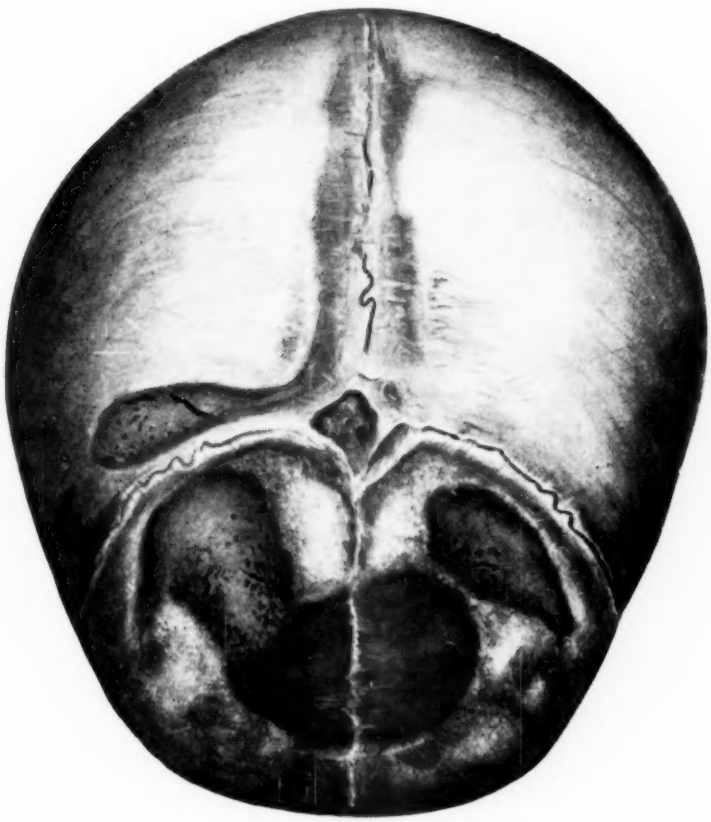


FIG. 18. Case 2.—Drawing of vault of skull, showing large areas of active erythropoietic tissue, the proliferation of which has caused thinning of the bone. This appearance is reminiscent of Cooley's anæmia of Mediterranean races; the child, however, was of English stock.

Summary.—A case of chronic fatal anæmia of aplastic type in a child aged 3½ years; a widespread reticulo-endotheliosis, which was of long duration and replaced areas of hæmopoietic tissue was found on histological examination.

Comparison and interpretation of the cases.—The outstanding features common to these four cases were the presence of severe anæmia and activity of elements forming part of the reticulo-endothelial system. The cases, however, varied considerably in their duration, in clinical features, and also in the type of activity displayed by the reticulo-endothelial cells, but it is

believed that, different as many of the aspects were, the nature of the original morbid process and of the tissues' reaction was fundamentally the same in all.

Reference is made later to the chief views held with regard to the function of the extensive reticulo-endothelial system, but for the moment, and for the purpose of correlating these cases, attention need be paid only to that principal function of the system, namely, phagocytosis and scavenging of waste material, the properties by which the components of the system were first recognized. The thesis is here put forward that the changes observed in the reticulo-endothelial system, though differing in form in the four cases, were reactive in nature; and further, that on the basis of the histological findings in this system cases differing widely in clinical characteristics can be correlated.

The first was the most acute case and clinically fitted into the subacute group of erythronoclastic (hæmolytic) anæmia, which has been described in Part V of this series. At the time of the first blood examination, so severe was the effect of the erythronoclastic process on the formative elements of the blood that an aplastic blood picture was presented. Later, during a remission, there appeared a somewhat regenerative picture, which could be accepted as one of a von Jaksch's syndrome. This improvement was unfortunately not maintained and an aplastic state again supervened. Though there was definite proliferation of reticulum cells which appeared to be fixed in the tissues, the outstanding feature was the production of free wandering histiocytes, or macrophages, the appearances of which corresponded in almost every detail with those of certain fixed cells, namely, reticulum cells and cells lining the lymph sinuses, which also were increased in number. The conclusion could not be evaded that these prominent histiocytes were being actively produced from those fixed cells: a view which is in accordance with that usually accepted of the origin of histiocytes. Further, the striking phagocytosis of red cells which the histiocytes displayed, revealed their function: they were engaged in scavenging, and not in the production of blood cells There remains the question whether this phagocytic activity was the cause of, or the response to, the red cell destruction and consequently the anæmia. At present the answer cannot be certain, but, since we know that hæmolysis of erythrocytes may occur so suddenly in some cases that only a direct injury of them seems conceivable, it is probable that in this case also, the primary damage was one of hæmolysis or erythronoclasis, and that the reticulo-endothelial activity was mainly reactive and consequent upon the original injury. It is probable that, as records of histological examinations on cases of relatively acute erythronoclasis accumulate, it will be found that activity of the reticulum cells and phagocytosis are outstanding features.

The second case clinically appeared similar, but the damage to the erythrocytes and their precursors was more chronic and regeneration was

more active than in Case 1: in other words, hæmolysis of mature erythrocytes was relatively greater and erythronoclasis relatively less. The erythropoietic tissues, however, failed ultimately to meet the strain and a less regenerative blood-picture ensued. Histological examination revealed the existence of much abnormal erythropoiesis, for many nucleated red cells were found in the spleen and lymph glands, but again the outstanding features were the swelling and proliferation of reticulum and endothelial cells. Here, too, it is possible to consider that these were due to the activity of these cells in clearing up the debris of lysed red cells, and in phagocytosis of abnormal forms produced by a hæmopoietic tissue, which was not only adversely affected by the erythronoclasis but was also attempting to make good a continuous and excessive loss of erythrocytes from hæmolysis.

The third case showed a fairly typical von Jaksch's syndrome and, as regards the anæmia, the course had been longer than the first two. Acute pneumonia developed and the consequent strong myeloid reaction complicated the blood, and especially the histological, pictures. The latter, apart from myeloid reaction, displayed a considerable proliferation of the splenic reticulum, which accounted for most of the great increase in size of the organ. This proliferation showed throughout a greater proportion of fixed cells, and the production of free histiocytes was less than in the two preceding cases; there was also an increase in reticulum fibres, and elongated forms of cells preponderated. Similar but considerably smaller areas had been found in the second case. The features were that of an activity of longer standing, and the increase in spindle forms of cells and reticulum fibres was analogous to the increase of fibrocytes and collagenous fibrils as organizing inflammatory tissue grows older.

Again in this case evidence of abnormal erythropoiesis was found, especially in the presence of many normoblasts in the splenic pulp. Elsewhere, evidence of activity of the reticulo-endothelial system was confined to the hepatic sinusoids and lymph sinuses, in which phagocytic histiocytes were numerous. The stimulation to these cells lay, no doubt, partly in the intense terminal infection, but also may have been due to the erythronoclastic process. The changes in the spleen appeared to be of longer standing; they doubtless denoted a milder but more chronic form of blood destruction than in the first two cases.

The fourth case was clinically different from the others. At the time of the first examination a few normoblasts were found and this formed the chief evidence in favour of a diagnosis of von Jaksch's anæmia, tentatively held for some time until the aplastic blood condition developed. Ultimately, the prolonged course, the outstanding hæmorrhagic tendency of the severe anæmia, the aplastic state of the blood and the absence of any definite increase in bilirubinæmia, seemed to exclude any connection with hæmolytic anæmia. However, the subsequent histological examination revealed that, as in the other cases, the reticulo-endothelial system was grossly affected: there was enormous proliferation of reticular cells and fibrils not only in

the spleen and lymph glands, but in the bone marrow also. Now in such diseases as malaria and kala-azar the early activity of the reticulo-endothelial system is of a cellular type, and this proceeds to the development of dense reticular and fibrous tissue. It appears, then, highly probable that the state of affairs found in our fourth case represented the ultimate development of reticulum cell activity that had long passed through the stages observed in the other three cases: again it was analogous to the development of fibrous tissue from a fibroblastic tissue. The widespread replacement of hæmopoietic by reticular tissue explained the development of the aplastic state of the blood.

On the basis, therefore, that the outstanding morbid change found after death affected the reticulo-endothelial tissue, there seems justification for classifying this obscure case with others, in which there were good clinical and hæmatological reasons for the diagnosis of hæmolytic or erythronoclastic anæmia. Accepting this hypothesis we may regard this case as illustrating one mode of termination of erythronoclastic anæmia.

We are now in a position to consider the modes by which erythronoclastic anæmia may develop. The initial blow may fall most heavily on the mature erythrocyte, leaving the erythropoietic tissue but little affected; in such a case the early blood picture will be regenerative. Should the bone marrow also suffer heavily, the blood picture will naturally be aplastic or anhæmopoietic. In either case there will be reticulo-endothelial activity, probably chiefly in the production of histiocytes, designed to clear up debris from the blood destruction, and also to destroy immature and unsuitable red cells produced by the affected marrow. If the erythronoclastic process continue, it is likely that it will affect the marrow to greater or less degree, and therefore the stimulation of the reticulo-endothelial system will be prolonged. There will be enlargement of the spleen, liver and lymph glands from the cellular proliferation, while the blood-picture will be regenerative or not according to the strength of the marrow's response. Another factor which will affect the degree of response, is the existence or not of embryonic hæmopoietic foci, at the time of the commencement of the erythronoclasis. If these are present, for example, in the liver and spleen, they, along with the marrow, will attempt to make good the loss of blood cells and thus remain in activity instead of fading out of existence, as is the normal course in late ante-natal and early post-natal life. This aspect of the subject has been dealt with in Part IV of this series.

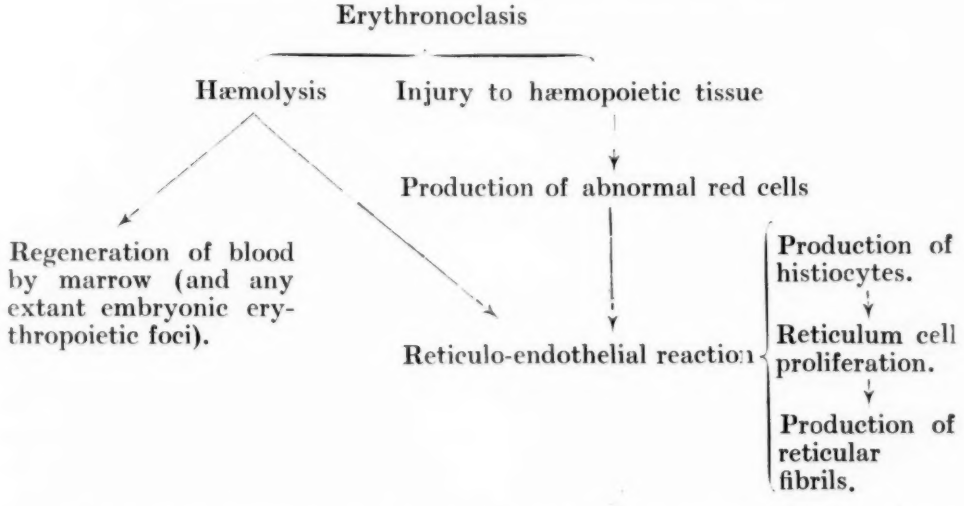
Finally, it appears that, if the erythronoclasis is relatively mild and yet prolonged in its action, the reticulo-endothelial system may maintain its reaction to the blood destruction and abnormal formation for so long, that it advances to extensive proliferation and the production of much reticular tissue; this may actually replace hæmopoietic tissue and so form a further contribution towards a state of anhæmopoiesis. Our fourth case is an example of this, and seems to represent the end result of a prolonged series of changes which began with erythronoclasis.

Owing to the confusion which has existed on the subject of von Jaksch's syndrome, it is difficult to find a convincing description of its histological changes. The presence of numbers of nucleated red cells in the spleen is accepted widely, and some authors mention the occurrence of the embryonic erythropoietic foci in the liver. The reticulo-endothelial reaction has come in for little attention, but it is referred to by Aschoff[1] and McNee[2]. Doubtless the swollen reticular cells have often been regarded as erythrogonia or the most primitive progenitors of hæmoglobiniferous cells, rather than the active participants in a reactive process. It is possible that some of the large cells, which Luzet[3] described in the first adequate description of the disease, were actually histiocytes and not erythrogonia.

From the description given it is obvious that the histological features of the so-called von Jaksch's anæmia, which we have regarded as a subchronic erythronoclastic anæmia, may be extremely varied and the changes will depend on: 1, the degree of response on the part of the marrow; 2, the existence or not of extramedullary embryonic centres of erythropoiesis; and 3, the reticulo-endothelial reaction, the type of which will largely depend on the duration of the morbid process.

In a recent annotation in the *Lancet*[4] criticism is offered of the suggestion made in Part V of this series that von Jaksch's anæmia should be regarded as a subchronic hæmolytic anæmia, on the grounds that the 'conclusions were based upon an analysis of a small group of cases with no post-mortem reports.' We regret that the number of cases of this syndrome available for study is so small, but we think that the pathological investigations contained in this paper afford strong evidence in support of our suggestion.

SCHEME OF EVENTS IN ERYTHRONOCLASTIC ANÆMIA.



Histological features of the reticulo-endothelial activity.—The features of the histological changes observed may be conveniently summarized here.

In the early stages of the reaction (e.g., Cases 1 and 2), there are swelling and proliferation of reticular cells of the spleen and lymph glands, and of the cells lining the hepatic capillaries and the lymph sinuses. In the sections of normal tissues stained with hæmatoxylin and eosin, these cells present an oval, triangular or even somewhat stellate nucleus, which stains rather darkly and uniformly, and which is of only moderate size, about 5μ in length. The cytoplasm is eosinophilic, and its tapered processes extend inconspicuously into the ground-work and often join the reticulum fibres. By suitable staining the ultimate union of these fibres with collagen bundles can be traced. The cell is generally not prominent. When such cells become active and proliferate they become much more conspicuous. The appearances of the nucleus are then characteristic: it is large, frequently 8μ in diameter, and often indented or even lobulated in shape; it stains rather faintly blue and the nuclear margin is delicately drawn; nucleoli are frequently not present and chromatin deposits are few, fine and irregularly scattered, and sometimes a network of slender threads can be made out. Large nuclei with an almost colourless interior are commonly found. Such characters can easily be made out in an active reticulum of a lymph gland or amongst active Küpffer cells, where normal individuals are still present with which comparison can be made. The size of the cytoplasm increases frequently up to a diameter of 10 and 12μ in sections, and forms over 20μ may be encountered; the cytoplasm is faintly eosinophilic and sometimes slightly granular. Large cells appearing free in the tissue spaces are seen to have features identical with the fixed ones; and, though phagocytosis varies from case to case, ingested inclusions, often lying in vacuoles, are found. The identification of these ingested cellular remnants, etc., is important, since it reveals the function of the free and fixed proliferated cells with certainty, and provides the weightiest reason for interpreting the reticulo-endothelial activity as reactive to a morbid process (such as abnormal blood formation and destruction) rather than as formative of different types of blood cells.

In the lumina of the lymph channels free cells similar to the above are often seen in large numbers, and cells partially attached to the walls. These cells may show degenerative changes, such as poor nuclear staining and a foamy cytoplasm. As far as the lymph channels are concerned the picture is similar to that so commonly seen in lymph glands draining an inflamed area. In these cases the cells lining the venous sinuses of the spleen have not been prominent or greatly increased in numbers, but proliferation and desquamation of this type of cell has been seen in myelosis (Part VIII), Banti's disease and acute infections. The numerous phagocytic histiocytes in the tissue spaces and sinuses, and the swollen lymphatic sinus and reticulum cells are characteristic and their features are easily recognizable. The only cell with which the last are likely to be confused is the fibroblast. Differentiation is usually possible on architectural grounds, but in individual cells there is often some difference in the appearances of the two types: the fibroblast usually shows a more regular contoured, but still lightly staining,

nucleus, often containing nucleoli; its basi-chromatin is in the form of a fine dust-like deposit[37] and does not exhibit the tendency to net formation. It might be noted here that there is strong evidence for the contention, which Maximow has long supported, that the histiocyte or polyblast may develop as a fibrocyte and take part in the formation of fibrous tissue, but it is by no means certain that the converse is true: that fibroblasts or fibrocytes may produce histiocytes.

In the late stages of the process, as exemplified in Case 4, there is seen to be a great increase in the fixed proliferated reticulum cells, which have now produced many fine reticulum fibres. These may be condensed in scattered areas into the form of knots, which with ordinary staining may fail to reveal a reticular character but are shown by silver stains to be composed of closely packed reticular fibrils. Case 4 showed these clearly. Further features of this late stage are the increase of frank fibrous tissue, and the absence of a great number of free histiocytes.

In the early stages an increased deposit of hæmosiderin, as revealed by the Turnbull-Huecke method is usually found, but this is not a feature later in the process. Along with this reticulo-endothelial activity various grades of erythropoiesis are found; the cytological features of the embryonic type have already been referred to in Parts IV and VIII and those of normoblastic type are too well known to require description. It may be noted, however, that normoblasts may be scattered widely in the tissues; large numbers were found in the lymph glands and even in the lymph follicles of the second case.

It is thus seen that in the development of the histological picture, a sequence of appearances from a cellular to a reticular fibril formation occurs, and this has many points of similarity to the sequence of changes in an inflammatory area proceeding to reparation.

The reticulo-endothelial system.—We owe our first and most valuable conceptions on the integrity and role of the widespread elements of the reticulo-endothelial system to Aschoff and his co-workers. The idea of the essential unity of the different components is largely based on the results of intra-vitam staining, and Aschoff[1] gave the following as an ascending series of intensity of staining: 1, endothelial cells of blcod and lymph vessels; 2, fibrocytes; 3, reticulum cells of splenic pulp, lymphatic cortical nodes and pulp; 4, reticulo-endothelial cells and sinuses of lymph nodes, blood sinuses of spleen, Küpffer cells of liver, capillaries of bone marrow, adrenal cortex and hypophysis; and 5, histiocytes. He considered that 1 and 2 may be excluded from the reticulo-endothelial system on account of their faintness of staining. Kiyono designated the reticulo-endothelial cells as histioblasts, because they gave rise to free cells, resembling histiocytes. The various cells of the system ingest foreign particles, such as colloids, bacteria, cellular remnants, and ' fix ' toxins such as those of diphtheria and tetanus; on this account a large role in immunity reactions has been ascribed to them. Aschoff has referred to erythro-phagocytosis by the system in various conditions, but especially in experimental arseniuretted hydrogen poisoning

in birds. Much work has been devoted to following the fate of the non-ferrous portion of the hæmoglobin, and it is now accepted that the reticulo-endothelial system plays an essential part in the production of jaundice. The epithelioid cells of tubercle, lepra cells, characteristic cells in rhino-scleroma, sporotrichosis, Gaucher's disease and other morbid processes, are either histiocytes or other reticulo-endothelial cells.

It is to be expected that such an extensive combination of cells may react strongly to certain stimuli; an example is found in typhoid fever, where the endothelial cell activity has been noted by Mallory and more recently has been studied by Schmidt[5] and again by Graff[6]. Their descriptions and illustrations of cells correspond closely with those already given under the case records. Goldzieher and Peck[34, 35, 36] have shown how the reticulo-endothelial cells of the spleen and liver react in infectious conditions in man and experimental animals; the illustrations of their papers show cytological features similar to those of the present cases. In typhoid fever and also in ulcerative endocarditis there is an increase of monocytes in the peripheral blood. This in itself is strong evidence for the origin of circulating monocytes from the reticulo-endothelial system, an opinion held by many, and supported by Garrod and Hadfield[7] in their recent excellent review. This rôle, however, is disputed by such an authority as Naegeli, who has long contended that the monocyte is a variant of the myeloid series. It is probable though, that some of the cells, placed in the group of monocytes, are immature metamyelocytes, which have a similar shape but which contain granules and are certainly myeloid cells. Aschoff and Kiyono found that some, but not all monocytes, were stained intra-vitally and their opinion appears to be that all blood monocytes have not the same origin, but that many are histiocytic and derived from the reticulo-endothelial elements.

Dameshek[8] has recently contributed a valuable review on the appearance of histiocytes in the peripheral blood. He concluded that the blood monocyte is a variant of the histiocyte which rarely circulates in the peripheral blood, and both are direct derivatives of the reticulo-endothelial system.

If blood monocytes are derived from the reticulo-endothelial system, the question naturally arises why they are not increased in all conditions in which the system is active. The answer is uncertain; but as the above observations show, the reaction of the reticular tissue varies, sometimes producing mobile histiocytes and at other times an increase of apparently fixed cells and reticular fibrils. Moreover, the sphere of activity of histiocytes is in the inner organs, where they may be seen assiduously ingesting cells and debris as in Case 1. Kiyono traced the entrance of reticulo-endothelial cells into the circulation and thence to the lungs, where they were filtered off. It is thus possible that histiocytes entering the circulation are soon removed, and that those seen in a film of the peripheral blood have only just entered the stream and normally would have been rapidly filtered off. The cytological appearances of many blood monocytes

are so similar to those of tissue histiocytes and sessile reticulo-endothelial cells, that it is difficult to escape the conclusion that they are the same type of cell. In addition to typhoid fever and ulcerative endocarditis, malaria and kala-azar, in which the reticulo-endothelial system is active, show a monocytosis. Monocytic leukæmia, or leukæmic reticulo-endotheliosis, is another condition in which large numbers of circulating monocytes are found. A case of this rare condition has recently been reported by us elsewhere[9], and its study supported the contention that circulating monocytic, or histiocytic, cells are derived from the reticulo-endothelial system and, if the system be affected by a leucotic type of process, may emigrate in large numbers.

There is thus some justification for concluding that the circulating monocyte is a direct derivative from certain elements of the reticulo-endothelial system.

The other rôle of the system, accepted by many, is that it may function, either obligatorily or vicariously, as a parent in post-natal life to all types of blood cells. This alleged and comprehensive rôle is one of the most vexed of hæmatological questions, and the evidence for it is much less certain than that for the scavenging and immunological functions. It is discussed in a later section of this paper.

Reticulo-endotheliosis.—Of recent years some cases, often under the above title, have been published mainly by German workers, and reference will now be made to some of these.

Letterer[10] published one case which has points of similarity to the present cases. The age of the patient was 6 months; the degree of anæmia was only moderate: red blood cells 5·6 million, hæmoglobin 65 per cent., white blood cells 26,000, with neutrophil polymorphonuclear cells accounting for 65 and monocytes for 8 per cent. Areas of sepsis, gangrene and petechiæ were present, and the duration of the illness before the fatal termination was 10 weeks. At autopsy an abscess of the axillary glands and small pea-like abscesses in the mediastinum were found, with enlargement of the spleen, liver and lymph glands. Histological examination revealed extensive proliferation of large pale histiocyte-like cells from the splenic and lymphatic reticulum and also from the Küpffer cells and marrow reticulum cells; small foci of necrosis in the midst of the cellular aggregations were found. Letterer compares his case with those of Pentmann[11], Borissowa[12], and Goldschmid and Isaac[13], which occurred in adults; and appears to favour an infective hypothesis of the origin of the disease. Letterer discusses Goldschmid's and Isaac's[13] case and emphasizes the fact, in which it differed from his own, that there was hyperplasia of endothelial cells lining splenic sinuses and liver capillaries rather than of the reticular cells.

The case of Schultz, Wermbter and Puhl[14] was that of a child aged $2\frac{3}{4}$ years, in which the diagnosis of von Jaksch's anæmia was suggested on clinical grounds; the objections to this diagnosis lay in a low white cell count of only 6,900, of which but 20 per cent. were lymphocytes, and normoblasts also were scanty. Petechiæ were present and, with increasing anæmia, death occurred. Histological examination of the enlarged spleen revealed a proliferation of reticular cells, in which were knots of fine reticular fibrils, and necrosis had apparently supervened in the centres of the larger knots. The description of the proliferated reticular cells and an illustration of a section of the spleen reveal a great similarity between this and Case 4.

Akiba[15] has reported the case of a female infant 10 months old, who was said to have been healthy until 1 week before admission, when fever, tonsillar sepsis, petechiæ, some splenomegaly and increasing anæmia developed; death occurred after 5 weeks.

Histologically, many large proliferated cells were present in the splenic pulp and lymph glands; aggregations of these cells, in which were small necroses and clumps of streptococci, were found. Akiba concluded that these changes were reactive to sepsis, and that in rare instances a strong response of the reticular cells may take the place of the usual myeloid reaction; further, that there was no justification for regarding the reaction as leukæmic in nature, and the title of aleukæmic reticulosis, as suggested by Letterer, could not be applied to his case. Another case described by Podvinec and Terplan[16] in a child of one year was similar in many respects to Akiba's case and showed only moderate anæmia; it was considered to be due to some general infection of the blood stream and the reticulo-endothelial activity was regarded reactive. Krahn[17] published the case of a child aged 5 years, in which occurred fever, profound anæmia with leucopenia, and enlargement of the lymph glands in the presence of sepsis; great proliferation of reticulum and endothelial cells in lymph glands and spleen, and necroses and microbic emboli were found.

The only account in English of reticulo-endothelial activity in children that has come to our notice, is one by Sherman[18], of an infant 11 days old, with erysipelas and jaundice. Blood culture yielded three hundred colonies of a hæmolytic streptococcus in 1 c.cm. There were great swelling and proliferation of capillary endothelium of the suprarenal glands, and the reticulum cells of the spleen and marrow, with intense phagocytic activity of the Küpffer cells. Guizetti[19] has recorded a case of a child aged 3 months, in which there were bleeding and considerable enlargement of the spleen and liver. Histological examination showed well marked proliferation of reticulum and sinus endothelial cells similar to that of the present cases. There was also a large cyst, apparently formed in proliferated reticular tissue in the humerus. This condition was considered to have been caused by some infectious process.

There are more records of cases in adults, some of which may be mentioned briefly here in order to show that different kinds of lesions affecting the system may occur. Goldzieher and Hornick[20] published two cases, one of which widely affected the bones, and the other was accompanied by pyrexia and anæmia; the authors review the subject. Wihman's[21] recent case was somewhat similar to Goldzieher's and Horaick's second case. Brill, Baehr and Rosenthal[33] reported three cases in adults showing marked generalized hyperplasia of the reticular cells of the lymphoid follicles, the illustrations are somewhat similar to those of glandular fever published by Pratt[29] and Bland[32].

While the present paper was in preparation a paper by Ross[22] appeared, which reported three cases in adults under the title of reticulosis: the third case was typical of generalized lymphadenoma, and the second was a case of reticulosis resembling Goldzieher's and Hornick's second case and Tschistowitsh's and Bykowa's[23] case. From the description of the first case, however, it appears very probable that it was a case of chronic aleukocythæmic lymphadenosis accompanied by reticular reaction, and the photomicrographs show a type of lymphoblast, with somewhat large and irregular nuclei similar to those described in Part VIII (p. 303) as occurring in lymphadenosis in children. Ross favours Maximow's views on the functions of reticular syncytium, as giving origin either to cells which function as histiocytes or to cells which differentiate as parenchymatous myeloid or lymphoid cells. This view of the multipotent functions of the reticulo-endothelial system in post-natal life is discussed in another section.

Terplan and Mittelbach[24], and Sachs and Wohlwill[25] have published under the title of 'lymphogranuloma,' cases in adults, in which a general and diffuse proliferation of the reticular tissue, sometimes lacking the typical structure of Hodgkin's disease, occurred; in some of these a tuberculous infection was present.

Roulet[26] has recently put on record 10 cases of 'retothelsarkom,' in which invasive properties were marked, and Komocki[27] has contributed similar cases to the literature. Roulet's paper is beautifully illustrated and shows types and grades of reticular cell proliferation. Paine[28] has recorded a case of hæmendothelioma of the spleen. This type of case appears to exemplify a focal malignant neoplasm of the reticular cells.

Though many writers are as yet unwilling to accept the occurrence of leukæmic reticulo-endotheliosis, there is a good deal of evidence that it may occur. An example, together with a review of cases, was recorded by us[9] recently. Further, aleukæmic types of reticulo-endotheliosis are claimed. It is not always clear what is meant by this qualification: whether simply an aleukæmic type or phase of a reticulo-endotheliosis that is essentially leukæmic (or leucotic) in type, or a reticulo-endotheliosis that is not essentially leukæmic or leucotic. Until the generalized reticulo-endotheliosis or reticuloses of obscure origin, for example, the cases of Tschistowitsch and Bykowa[23], have been further studied, it will be difficult to classify certain cases, just as it is still difficult always to separate cases of extreme leucocytic reaction from leucosis. Many workers, of course, would not attempt a differentiation, since they hold with Sternberg that acute leucosis is a form of reaction to severe infection. However, as suggested in our paper above mentioned, it is reasonably certain that cases of leukæmic reticulo-endotheliosis do occur and show leukæmic monocytes or histiocytes in the peripheral blood; and apart from this feature they may be identified by a widespread infiltration, as opposed to merely a proliferation, of similar cells in the tissues. It is reasonable to expect that aleukæmic forms or phases of this essentially leukæmic (or leucotic) type of reticulo-endotheliosis should occur. It appears that most of the cases in children to which reference has been made, e.g., Akiba's[15], are non-leucotic, but reactive in nature to some form of infection.

Classification and nomenclature.—It is thus evident that a variety of changes occur in the reticulo-endothelial system and sometimes these are more or less confined to one or more components. Some forms of activity appear to be reactive, while others are neoplastic. We may classify the morbid processes, affecting the system in the following way:—

(A) REACTIVE.

(i) To blood destruction.

(ii) To sepsis and infection.

(a) Glandular fever:—reticulo-endotheliosis of lymph glands, Pratt[29].

(b) Typhoid fever.

(c) Infection (Akiba, Sherman).

(d) Granulomatosis:—e.g. Hodgkin's disease.

(iii) To chemical abnormalities:—Gaucher's disease[30], etc.

(B) FOCAL NEOPLASTIC.

Reticuloma (Roulet, Komocki).
Hæmendothelioma (Paine).

(C) LEUCOTIC.

Reticulo-endothelial leucosis: leukæmic or aleukæmic reticulo-endotheliosis; or monocytic or histiocytic leukæmia.

The above sub-headings are intended to be only exemplary and not comprehensive.

The term reticulo-endotheliosis has then to serve for conditions which may differ in nature as widely as reactive hyperplasia and neoplasia. For this reason the qualification ' leucotic ' is suggested for indicating a type of reticulo-endothelial activity which appears to be analogous to the leucoses. A further alternative in nomenclature for this leucotic type of reticulo-endotheliosis is the term ' reticulo-endothelial leucosis ' to contrast with myeloid and lymphatic leucosis. Further, it is to be expected that leucotic reticulo-endotheliosis, or reticulo-endothelial leucosis, may be leukæmic or aleukæmic.

For certain cases the more restricted term ' reticulosis ' seems more fitting (Ross, Letterer and others); but in most both types of components of the system, reticulum and sinus endothelial cells (littoral cells of Siegmund, Ross) are found to be active in greater or less degree, and, therefore, the more comprehensive term ' reticulo-endotheliosis ' is convenient for general use and classification.

Genealogy of the blood cells.—Speculation on the origin of the blood cells is interesting and of some importance, for, if we can be certain of the source of the various types of cells we shall better interpret the changes in the peripheral blood, especially those noted by the differential count of the white cells. The present study, and those recorded in Parts IV and VIII of this series, have indicated that:—

1. Immature leucotic cells usually display characters which are different in the two chief series of blood cells, i.e., myeloblasts are usually distinguishable from lymphoblasts.

2. Myelosis and lymphadenosis each present a distinctive histological structure.

3. A leucotic process is pure, i.e., histologically any given case of leucosis presents the architectural and cytological features only of its type. The cases recorded in Part VIII did not support the hypothesis of mixed types.

4. The reticulo-endothelial system shows activity in such widely different conditions as leucosis, erythroblastosis and erythronoclasis; and this can be better interpreted as reactive to, than as formative of, leucotic cells.

5. The reticulo-endothelial system when active produces histiocytes, and the blood monocytes are essentially the same type of cell.

Piney[31] has given an excellent summary of the chief views held on the origin of the blood cells. The main contention lies between what has been called monophyletism and polyphyletism: supporters of the former creed hold that in post-natal life a cell which is multipotent in its genetic capabilities exists, and can therefore give rise to cells of different types, e.g., myeloid and lymphatic. This cell is called the lymphoidocyte or Ferrata's hæmocytoblast. Naturally, in the embryo the different blood cells have a common ancestor at some period; although there is much discussion as to the relation of certain cells in the primitive blood islands, this aspect

of embryonic hæmopoiesis need not detain us. The polyphyletic view holds that only unipotent stem cells are present in post-natal life, i.e., that myeloid cells are produced only from myeloid tissue, etc. Piney considers that the reticulo-endothelial tissue is multipotent but that its immediate offspring, as soon as produced, is endowed with fixed potentialities with regard to its future development, i.e., it is a myeloid, lymphatic, or other cell. Ferrata claims that tissue that is hæmohistioblastic, probably the reticulo-endothelium, produces hæmocytoblasts, which produce different types of blood cells and may circulate in the blood stream.

Now as regards the monophyletic view, a lymphoidocyte or hæmocytoblast in an anaplastic leucosis should not show differentiation into either a myeloblast or a lymphoblast, but, if the view of its origin from reticulo-endothelium is correct, the characters would be histiocytic in type. Although the characters discerned over a range of leucotic cells have shown differences between myeloblasts and lymphoblasts, as recorded in Part VIII of this series (p. 303), it must be admitted that each and every cell did not show such distinctive features that it could be classified with certainty. But the most immature cells certainly did not display features resembling those of histiocytes or monocytes. The fact that myelosis and lymphadenosis each present a distinctive histological structure suggests that each type of leucotic cell is distinct from the other, and therefore probably unipotential in genetic capabilities. The third finding too, that mixed leucoses do not occur, though some observers, e.g., Downey, claim that they are rarely encountered, seems to have similar implication.

Of our results those which have most bearing on the subject of the genealogy of the blood cells relate to the activity of the reticulo-endothelial system (see paragraphs 4 and 5 on the previous page). In addition, we have recently recorded[9] a case in a child, in which there appeared to be a leucosis of the reticulo-endothelial system, in which numbers of histiocytes or monocytes were produced. These cells showed no resemblance to myeloblasts or lymphoblasts, nor any tendency to develop in the direction of either. If monophyletism were true, it would be expected that such a leucosis would show cytological features less distinctive of histiocytes and a tendency to produce a histological structure of myelosis or lymphadenosis or both.

In the lymphatic follicle lymphocytes, which are one of the chief types of blood cells, are seen lying in close proximity to a component of the reticulo-endothelial system, e.g., the so-called germ centre. In such a region the study of the relationships of the two types is comparatively easy. Now a cogent argument against the formation of lymphocytes from reticulo-endothelium in post-natal life rests on the fact that the germ centres are not active in lymphadenosis, where there is a gross proliferation of lymphoblasts. Yet in conditions in which there is the greatest activity of the reticulo-endothelial, but not of lymphocytic, cells, as in erythronoclasis and chronic inflammation of lymphatic tissue, these germ centres also are actively proliferating.

Many of the views on the development of blood cells have been based on the alleged tracing of transition forms between recognized types of cell. This method has its uses, but is particularly open to fallacies, for in blood films or sections individual cells can usually be met that could be interpreted as transition forms between almost any types. For example, a series of cells might be chosen from most blood films or tissue sections showing ' transition ' from lymphocyte to monocyte, and from monocyte to myelocyte, and thence to polymorphonuclear granulocytes. Now the appearances of the fixed reticulo-endothelial cells lend themselves readily to such interpretation: in myelosis or lymphadenosis, cells can be seen which taken individually appear to represent stages of transition from the active and swollen reticulo-endothelial cells to either myeloblasts or lymphoblasts. It is no doubt partly for this reason that active reticulo-endothelial cells in post-natal life have often been interpreted as forming the cells which lie in their neighbourhood. As has been emphasized already, the chief function of the reticulo-endothelial system seems to be somewhat different: it is that of a general scavenger, which can be expected to resent the intrusion of foreign cells and attempt to destroy them. It seems incongruous to suggest that the reticulo-endothelial system is at one and the same time both formative and destructive of immature or stem cells. An interpretation, therefore, which covers all our observations of the activity of the reticulo-endothelial system in post-natal life in the conditions of leucosis, erythroblastosis and erythronoclasis, is that this activity is reactive to the morbid process, abnormal blood cell formation or destruction. Thus the system in post-natal life cannot be regarded as a progenitor of the various types of blood cells.

In so far, therefore, as these studies bear on the subject, since we have found no evidence of an indifferent cell, the hæmocytoblast, and the reticulo-endothelial system has not seemed to take part in the formation of myeloblasts, lymphoblasts, and erythroblasts, we are bound to accept a polyphyletic view of events in post-natal life, and conclude that myeloid cells are reproduced by myeloid tissue, lymphocytes by lymphatic tissue, erythrocytes from erythroblastic tissue, including normoblastic, and histiocytes and monocytes from reticulo-endothelial tissue. It may be added that the above scheme does not exclude the possibility of another line of development of the histiocyte, and fibroblasts, from the lymphocyte; this view has been put forward by Maximow, Bloom and others, and is based on careful and extensive experimental work. Evidence to suggest that the histiocyte may take part in the formation of fibrous tissue, i.e., become a fibrocyte, is not wanting in many common pathological processes, as in the resolution of inflammation, the fibrosis in a tuberculoma, etc., but, as mentioned previously, the converse change probably does not take place.

Summary of clinical features.—The four cases here presented varied considerably in their clinical features at the period of observation. It is believed that they represented different stages and grades of severity of

erythronoclastic (hæmolytic) anæmia. The clinical aspects of this disease have been dealt with in Parts IV and V of this series, and there remains only to consider what appears to be a chronic form, or rather end result exemplified in our fourth case. We may summarize this clinical picture by noting that the age was about two years at the time of the first observation, there was a history of prolonged anæmia, possibly from birth; there was splenomegaly with a few petechiæ, and the blood examination revealed anæmia of moderate severity, with a somewhat high colour index and signs of slight regeneration on the part of the bone marrow. Thereafter the anæmia slowly increased, the hæmorrhagic tendency developed so that alarming hæmorrhages occurred, enlargement of the spleen and liver increased and the lymph glands became slightly palpable, and the blood-picture progressed to that of a severe aplasia of all the elements. A course such as this should at least raise suspicion that widespread reticulo-endotheliosis is supervening on chronic erythronoclastic anæmia.

Diagnosis.—This clinical picture is somewhat similar to that of Banti's disease or splenic anæmia of adult type. Clinically the age incidence is different, since Banti's disease is extremely rare in children under six or seven years of age. Hæmatemesis occurs in both conditions. In severe splenic anæmia the state of the blood is similar to that of our fourth case. Definite enlargement and hardness of the liver is somewhat in favour of splenic anæmia, whereas slight glandular involvement points towards a reticulo-endotheliosis. If splenectomy be carried out, histological examination should reveal points of difference. In three cases of splenic anæmia of adult type which we have examined pathologically there were dilated venous sinuses separated by thick well defined strands of fibrous, rather than reticular, tissue, and the cells lining the sinuses were somewhat prominent (see Fig. 17); there appeared to be some increase in reticulum cells also between the venous sinuses; Gandy-Gamma nodules were not present. Case 4 in our present series showed a proliferation which was much finer and produced separate strands and bundles of reticulum (see Fig. 12 and 13). The features of splenic anæmia correspond with those to be expected on the assumption that the cirrhotic process arises in some form of vascular disturbance especially operating in and through the venous sinuses.

The clinical course of familial hæmolytic icterus (acholuric jaundice) is, of course, entirely different. Histologically there is found some proliferation of the splenic pulp cells, but our cases have shown neither the swelling nor the proliferation of reticular fibres seen in Case 4.

Lymphogranuloma (Hodgkin's disease) presents many points of resemblance even in the histological features. It may rarely be generalized, as in some cases of Terplan and Mittelbach[24]. Usually a pleomorphic picture is present, and some if not all of the characteristic features, giant cell formation, increase of eosinophil and plasma cells, and necrosis are found. These features, together with the usually focal nature of the disease, enable a differentiation from a case such as our fourth to be made.

In glandular fever proliferation of the cells of the reticulum and of the central follicular cells in the lymph glands is considerable and resembles that discussed above [29, 32]. Anæmia is, however, absent and there is no evidence of hæmolysis or erythrophagocytosis; the spleen does not enlarge to any extent and the benign course assists in differentiation. The suggestion may be made, however, that cases of obscure reticulosis in adults, examples of which have been referred to, might conceivably commence with glandular fever which fails to resolve. So far as we are aware, no evidence for this has yet been produced.

The other types of reticulo-endotheliosis, e.g., storage and leucotic forms, have been mentioned elsewhere in this paper. The storage types present certain distinctive characteristics, into which there is not space to enter here. The leucotic type has been dealt with in another paper and is rare; our case showed a much more acute onset and shorter duration than our present Case 4.

Chronic or subacute myelosis and lymphadenosis may be accompanied by considerable splenomegaly and the clinical and histological features have been dealt with in Part VIII.

The above mentioned are, of course, only some of the many conditions which may be associated with considerable splenomegaly and a varying degree of anæmia, and especially diseases of parasitic origin should be considered before arriving at a diagnosis of reticulo-endotheliosis of the nature exhibited in Case 4.

Treatment.—The lines of treatment of the early and more acute stages have already been dealt with in the previous papers. The greatest hope lies in blood transfusion when anæmia is severe, though remission often sets in without obvious relation to any form of treatment, apart from general care and attention. With regard to the ultimate stage as seen in Case 4, the histological findings indicate that splenectomy might be beneficial, but this procedure might prove extremely hazardous and careful preparation of the patient would be essential.

Summary and conclusions.

1. Four fatal cases of severe anæmia in children are recorded. Clinically two were cases of acute or subacute erythronoclastic (hæmolytic) anæmia; one of the chronic form of this anæmia; and one of obscure nature. All resembled in greater or less degree the so-called von Jaksch's anæmia.

2. Histological investigation after death showed widespread activity of the reticulo-endothelial system in all. This varied in type according to the duration of the anæmia. Details of the histological findings are given. In two cases abnormal erythropoiesis was present.

3. It is suggested that this reticulo-endothelial activity is reactive to erythronoclasis or blood destruction and abnormal erythropoiesis, the latter being a response to an erythronoclastic process of obscure origin.

4. The syndrome known as von Jaksch's anæmia, is that of a regenerative phase, and but one of several phases, in the progress of erythronoclastic anæmia.

5. This phase may be followed by one in which the balance is upset, so that the reticulo-endothelial reaction outstrips the erythropoiesis and remains as the outstanding feature. This is accompanied chiefly by splenomegaly and an aplastic blood picture.

6. It is probable that some obscure and hitherto unclassified anæmias in children belong to this phase.

7. This and other histological studies in this series of papers suggest that reticulo-endothelial activity is reactive and not formative of blood cells. The bearing of this view on the question of the genealogy of the blood cells is briefly discussed.

9. Some recent cases of generalized reticulo-endotheliosis, chiefly recorded in the German literature, are briefly reviewed.

It is a pleasure to express my appreciation of the help given by my chief assistant, Mr. J. T. Hall, in the preparation of material, and by Mr. E. B. Brain in illustrating Parts VIII and IX; and to thank also the other members of the laboratory staff, on whom the burden of extra work has fallen.

REFERENCES.

(Articles marked * are accompanied by good illustrations.)

1. Aschoff, L., *Lectures on Pathology : Janeway lecture*, N.Y., 1926.
2. McNee, J. W., *Lancet*, London, 1931, i, 950.
3. Luzet, C., *Etude sur les anémies de la première enfance*, Paris, 1891, 89.
4. *Lancet*, London, 1933, ii, 432.
5. Schmidt, M. B., *Centralbl. Allgem. Path. u. Path. Anat.*, Jena, 1907, XVIII, 593.
*6. Graff, S., *Deutsches Arch. f. Klin. Med.*, Leipzig, 1917-18, CXXV, 352.
7. Hadfield, G., & Garrod, L. P., *Recent Advances in Pathology*, London, 1932.
*8. Damashek, W., *Arch. Int. Med.*, Chic., 1931, XLVII, 968.
9. Gittins, R., & Hawksley, J. C., *J. Path. & Bact.*, Edin., 1933, XXXVI, 115.
*10. Letterer, E., *Ztschr. f. Path.*, Frankfort, 1924, XXX, 377.
*11. Pentmann, I., *Ibid.*, 1915-16, XVIII, 122.
12. Borrisowa, A., *Virch. Arch. f. Path. Anat.*, Berlin, 1903, CLXXII, 108.
13. Goldschmid, E., & Isaac, S., *Deutsch. Arch. f. Klin. Med.*, Leipzig, 1922, CCXCI, 138.
14. Schultz, A., Wermbter, F., & Puhl, H., *Virch. Arch. f. Path. Anat.*, Berlin, 1924, CCLI, 519.
15. Akiba, R., *Ibid.*, 1926, CCLX, 262.
*16. Podvinec, E., & Terplan, K., *Arch. f. Kinderh.*, Stuttgart, 1931, XCIII, 40.
17. Krahn, H., *Deutsch. Arch. f. Klin. Med.*, Leipzig, 1926, 152, 179.
18. Sherman, I., *Arch. Path.*, Chicago, 1929, VII, 78.
19. Guizetti, H. V., *Virch. Arch. f. Path. Anat.*, Berlin, 1931, CCLXXXII, 194.
20. Goldzieher, M. A., & Hornick, O. S., *Arch. Path.*, Chicago, 1931, XII, 773.
21. Wihman, G., *Virch. Arch. f. Path. Anat.*, Berlin, 1931, CCLXXXII, 181.
*22. Ross, J. M., *J. Path. & Bact.*, Edin., 1933, XXXVII, 311.
*23. Tschistowitsch, T., & Bykowa, O., *Virch. Arch. f. Path. Anat.*, Berlin, 1928, CCLXVII, 91.
*24. Terplan, K., & Mittelbach, M., *Ibid.*, 1929, CCLXXI, 759.
25. Sachs, Fr., & Wohlwill, Fr., *Ibid.*, 1927, CCLXIV, 640.

*26. Roulet, F., *Ibid.*, 1930, CCLXXVII, 15.
*27. Komocki, W., *Ibid.*, 1924, CCL, 517.
28. Paine, C. G., *J. Path. & Bact.*, Edin., 1931, XXXIV, 139.
29. Pratt, C. L. G., *Lancet*, Lond., 1931, ii, 794.
30. Graham, S., & Blacklock, J. W. S., *Arch. Dis. Childh.*, Lond., 1927, II, 267.
31. Piney, A., *Diseases of the Blood*, 2nd. Edn., London, 1932.
32. Bland. J. O. W., *Lancet*, Lond., 1930, ii, 521.
33. Brill, N. E., Baehr, G., & Rosenthal, N., *J. Am. Med. Ass.*, Chicago, 1925, LXXXIV, 668.
34. Goldzieher, M. A., *Arch. Path.*, Chicago, 1927, III, 42.
35. Goldzieher, M. A., & Peck, S. M., *Ibid.*, 1927, III, 629.
36. Goldzieher, M. A., & Peck, S. M., *Loc. cit.*, 635.
37. Maximow, A., & Bloom, W., *Textbook of Histology*, Chicago, 1931, 75.

The above paper concludes the series of 'Studies in Anæmia' by Professor Leonard Parsons and his colleagues. The final Part on 'The hæmatocrit in clinical medicine' by Dr. R. Gittins has been unavoidably held over, and will appear as a separate paper next year. (Editors, A.D.C.)

LIPIODOL IN THE DIAGNOSIS OF CONGENITAL ŒSOPHAGEAL ATRESIA

BY

C. FRASER BROCKINGTON, M.D., D.P.H.,
Late Assistant County Medical Officer, Worcestershire,
AND
REGINALD LIGHTWOOD, M.D., M.R.C.P., D.P.H.,
Assistant Physician for Diseases of Children, Westminster Hospital.

(From the Hospital for Sick Children, Great Ormond Street, London.)

Two infants, aged 12 and 6 days at the time of death, were admitted to the Hospital for Sick Children, Great Ormond Street, with the history of 'going blue and suffocating' on attempting to take food. The injection of

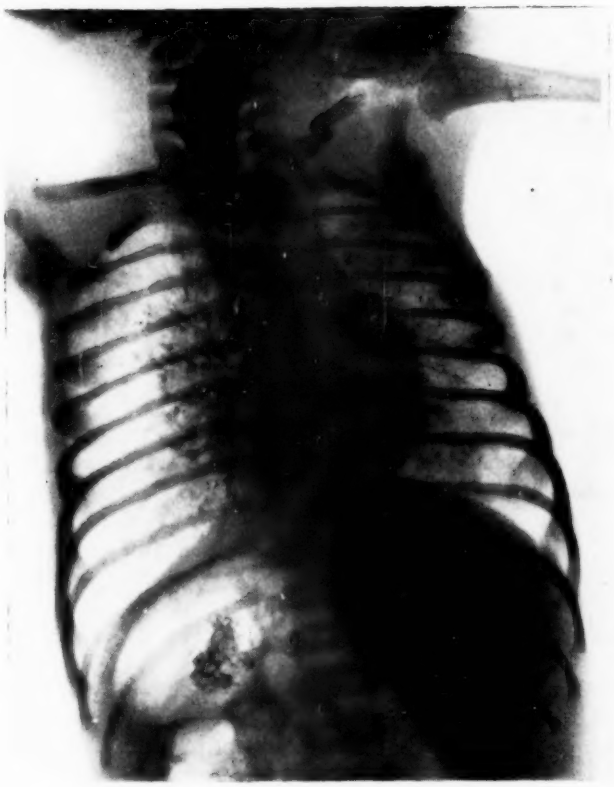
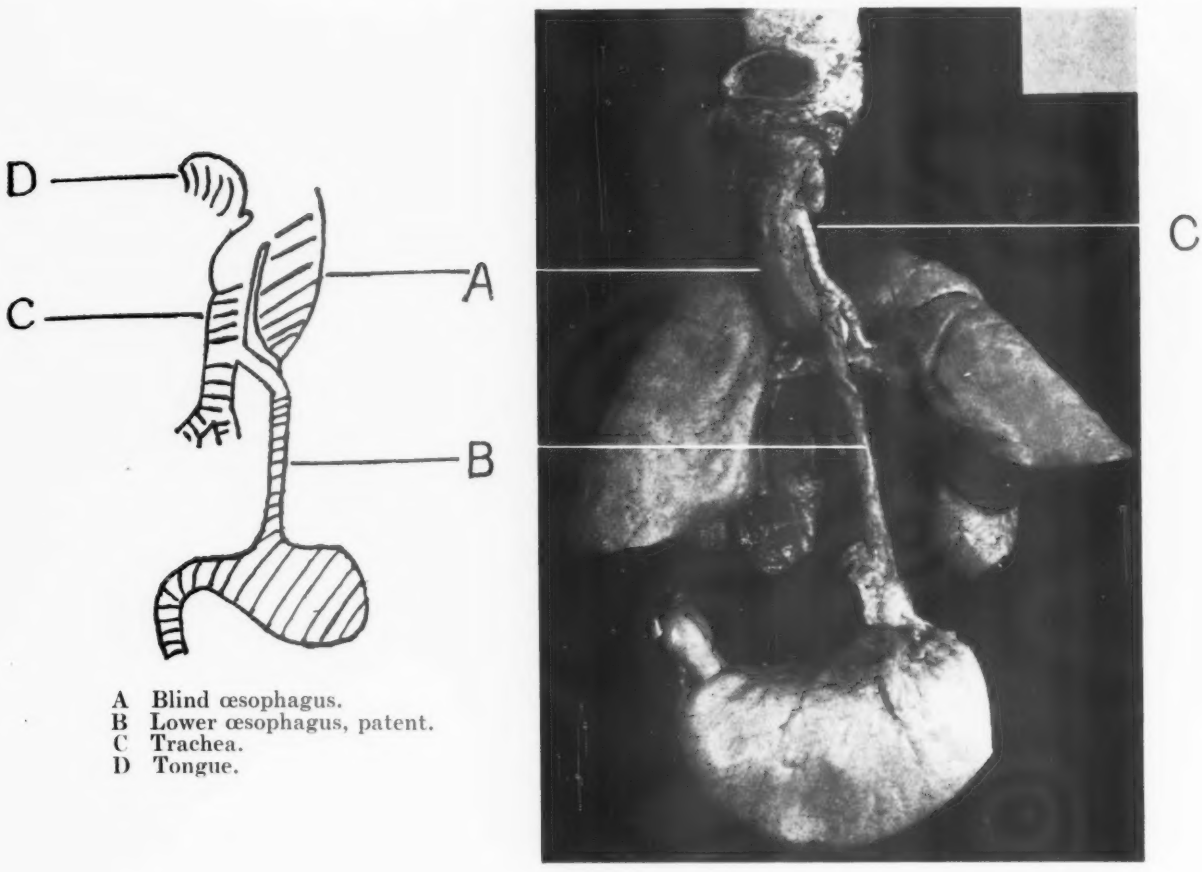


FIG. 1. Case 1.—The shadow of the blind œsophagus is seen above the level of the clavicles. Lipiodol, spilt back into the larynx, has passed down the trachea, has outlined the bronchial tree, and has also reached the stomach by way of a tracheo-bronchial fistula.

5 c.cm. of lipiodol into the œsophagus during life was successful in establishing by radiography the diagnosis of atresia of the œsophagus in both cases. In practice this may be performed with the aid of fluoroscopy. The accompanying radiograms demonstrate the conditions found on admission to hospital.



A Blind œsophagus.
B Lower œsophagus, patent.
C Trachea.
D Tongue.

FIG. 2. Case 1.—Above, the blind œsophagus is seen. Below, the œsophagus leads out of the trachea just above its bifurcation.

In Case 1 (investigated June, 1932), skiagrams during life showed a blind end to the œsophagus with a little lipiodol both in the stomach and in the lungs (Fig. 1). A post-mortem examination in this infant revealed complete atresia of the œsophagus with a communication extending from the bifurcation of the trachea to the lower portion of the œsophagus (Fig. 2).

It was thus evident that the lipiodol present in the lungs and stomach of this infant in the ante-mortem skiagrams had spilt over from the upper end of the œsophagus into the trachea, thus finding its way into the bronchial tree and, through the fistula, into the stomach.

In Case 2 (investigated October, 1932), the ante-mortem radiograms suggested complete atresia of the œsophagus (Fig. 3). It was not possible to obtain a post-mortem examination in this case, but post-mortem radiography after the injection of lipiodol into the trachea, and into the œsophagus from above and below, was sufficient to show the existence of complete atresia without tracheo-œsophageal fistula (Fig. 4).

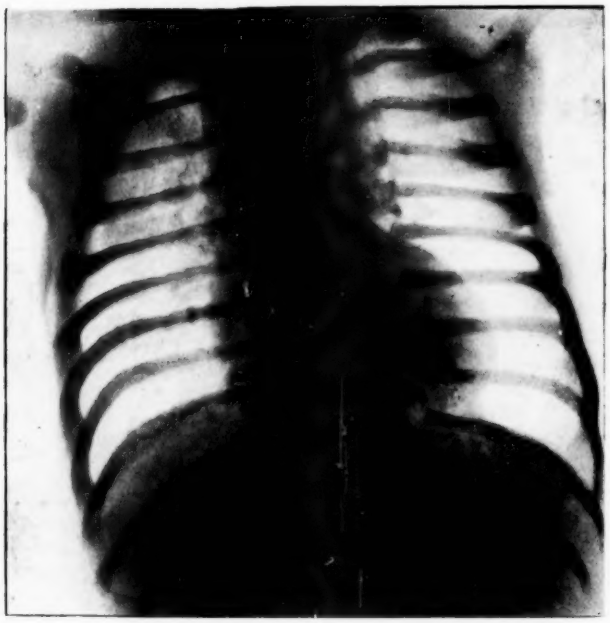


FIG. 3. Case 2.—Ante-mortem radiography. The œsophagus which is dilated, ends blindly at the level of the sixth costal cartilage.

Discussion.

This aid to the diagnosis of congenital œsophageal atresia, also reported upon by Reid[1] soon after the beginning of our work, is of more than academic interest. The clinician, confronted with a new-born infant presenting the symptoms of choking and cyanosis on feeding, may be required to give a definite diagnosis of congenital atresia, a diagnosis which carries with it an invariably fatal prognosis. Radiological confirmation of his diagnosis may be valuable. The expectation of life of the 250 or more cases[2] which have been reported since the condition was originally described by Durston[8] in 1670 does not, in the absence of surgical intervention so far considered inadvisable[6], exceed 13 days. It is of interest that the two infants reported here present examples of both types of congenital atresia known to occur[3, 7]. The first case is an example of the commoner variety, namely, atresia with tracheo-œsophageal fistula. This occurs in 84 to 92 per cent. of recorded

instances[2, 4], and only about 10 per cent (of which the second case is an example) consist of simple atresia without fistula. For a discussion of the probable mechanism producing atresia of the œsophagus in the newborn, reference may be made to the writings of Keith and Spicer[3] and of Sheldon[5].

We are indebted to Dr. Poynton for permission to publish these two cases, and to Dr. Shires for help in the interpretation of the radiograms.

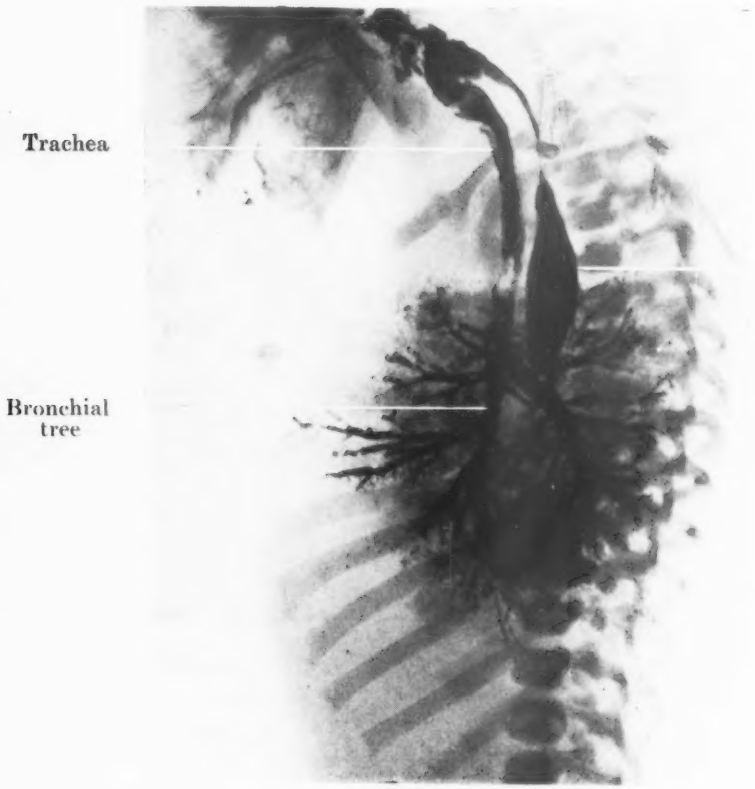


FIG. 4. Case 2.—Post-mortem radiography. First the blind œsophagus was filled with sodium iodide. Subsequently the bronchial tree was injected. If a tracheo-œsophageal fistula had been present some of the opaque fluid would have passed into the stomach.

REFERENCES.

1. Reid, M. D., *J. Pediat.*, St. Louis, 1932, I, 87.
2. Rosenthal, A., & Himmelstein, U., *Arch. Ped.*, N.Y., 1932, XLIX, 444.
3. Keith, A., & Spicer, *J. Anat. & Phys.*, Lond., 1907, XLI, 52.
4. Heumann, J., *Abt's Pediatrics*, Philad., 1st Edition, 1924, III, 406.
5. Sheldon, W. P. H., *Arch. Dis. Childh.*, Lond., 1926, I, 279.
6. von Reuss, A. R., *Dis. of Newborn*, Lond., 1921, 251.
7. Cautley, E., *Brit. J. Dis. Child.*, Lond., 1917, XIV, 1.
8. Durston, *Collect. Academ.*, Part. etrang, 1670, t. ii, 288.

DOUBLE AORTIC ARCH

BY

CHARLES E. SNELLING, M.B.,

AND

I. H. ERB, M.B.

(From the Hospital for Sick Children, and the Department of Pædiatrics, University of Toronto, under the direction of Dr. Alan Brown.)

Double aortic arch is a comparatively rare anomaly which has been discovered usually in the dissecting room or at autopsy. Most of the recorded cases have had symptoms of constriction of the œsophagus and trachea, resulting in death from broncho-pneumonia at an early age, but occasionally the condition has given rise to no unusual phenomena, and has been found in adult subjects. We report here a case of double aortic arch, which was diagnosed clinically as persistent right aortic arch with constriction of the œsophagus and trachea.

Case report.

M.S., a four months white female, was admitted to hospital on November 4th, 1932. The parents had noticed that the infant had breathed noisily since birth, and had had severe blue spells two weeks and one week prior to admission. The family history was of no consequence; the gestation was nine months; the birth weight was 6 lb.; the labour and neonatal periods were not abnormal.

The infant was breast fed. There was some regurgitation during and after feeding. Frequently the child had to stop nursing to get its breath. No cod-liver oil or orange juice had been given, but the child had been exposed to the summer sun. The noisy, rattling breathing, which was present from birth, had not been unduly alarming until two weeks before admission, when the child had a severe blue spell. Artificial respiration was necessary as the child was unable to get its breath for some time. A similar attack occurred one week later. The mother noted that the child had difficulty in drawing the air into the chest, because there was a recession of the ribs and abdomen when the child took a breath. This was made worse by excitement and crying. Nursing was frequently interrupted so that the child might get its breath. No inspiratory crow or convulsions had been observed. A brassy, dry, hacking cough had been present since two months of age.

On admission the child did not appear severely ill, though it was obviously breathing with difficulty. The throat was red: the right ear drum was bulging, and paracentesis was done. Difficulty with respiration, especially inspiration, was evident from the indrawing of the chest wall and an audible inspiratory stridor. The breath sounds were transmitted from the larger passages and were loud and wheezy in type. No other abnormal physical findings were noted. Direct laryngoscopy revealed nothing abnormal in the vocal cords, larynx or trachea as low as the third tracheal ring.

For the first 10 days in hospital varying pyrexia up to 104°, due to the upper respiratory infection, prevented any further investigation other than a roentgenogram of the chest, which revealed some peribronchial infiltration Two weeks after admission, when the infection seemed to be clearing, the child had a series of severe attacks of blueness for which artificial respiration

was required. It was noted that these occurred during or following feedings. Coincident with this the upper respiratory infection flared up. Barium was given and a roentgenogram of the œsophagus was made, showing a constric-

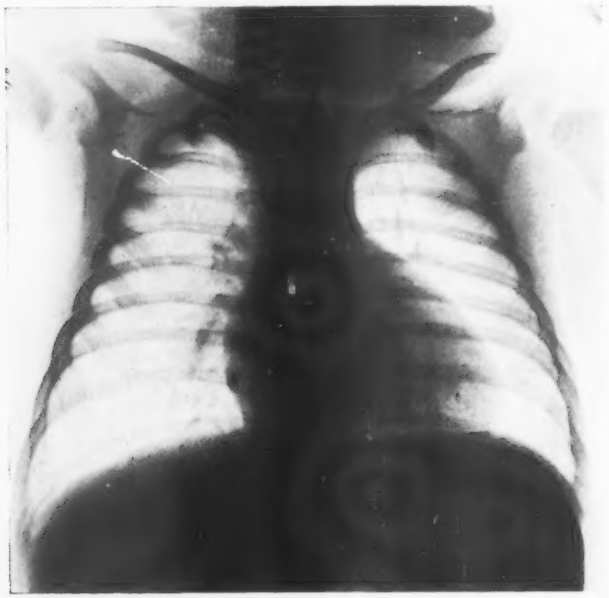


FIG. 1.

FIG. 2.

Radiograms showing a constriction of the œsophagus opposite the bodies of the third and fourth dorsal vertebræ.

tion opposite the bodies of the third and fourth dorsal vertebræ (Fig. 1 and 2). Below this was a ballooning of the œsophagus similar to that seen in

cardiospasm. The similarity of the roentgenogram and history to those of right aortic arch[1, 2] led us to advance the diagnosis of persistent right aortic arch, causing constriction of the trachea and œsophagus.

The upper respiratory infection progressed, broncho-pneumonia developed, and the infant died one month after admission.

Post-mortem report. The body was fairly well developed and poorly nourished. The skin was dry, pale, hung rather loosely and showed no superficial lesions. There was no superficial glandular enlargement.

The abdominal cavity and viscera appeared normal. In the thorax both pleural cavities were free from fluid, adhesions and pus. The thymus was normal.

The pericardial sac contained a normal amount of clear, straw-coloured fluid. The pericardium appeared healthy. The heart was not enlarged, and the valves and chambers were normal. It contained a small amount of dark red, poorly-clotted blood. The superior and inferior venæ cavæ entered the right auricle in the usual manner. The pulmonary artery was healthy and arose from the right ventricle dividing into right and left pulmonary arteries. The pulmonary veins entered the left auricle showing no abnormalities.

The aorta is described below with the trachea, bronchi, œsophagus and stomach. The lungs were salmon-pink and crepitant anteriorly. Posteriorly both showed considerable diminution in crepitation, especially in the lower lobes where none was elicited. In this area the lung was quite firm and of a greyish-red, mottled appearance. The bronchial glands were enlarged and red.

The liver, gall-bladder, spleen and pancreas appeared normal. The kidneys and genito-urinary tract were healthy. The duodenum, small and large intestine, were healthy throughout. There were no abnormalities of the mesentery. The scalp and calvarium were normal. The anterior fontanelle was depressed. The dura mater was smooth and pearly white. The lepto-meninges were not congested. The convolutions were well marked. The substance of the whole brain appeared normal. The ventricles were not dilated; they contained clear, colourless fluid. The intracranial venous sinuses were not thrombosed.

The right middle ear and mastoid antrum were filled with thick, yellowish pus. The right drum was opaque and had an opening in its posterior quadrant, which was covered over by pus. The left middle ear and mastoid antrum were similar to the right, except that the pus on this side was red. The opening in the left ear drum was still patent.

AORTA, TRACHEA, BRONCHI, ŒSOPHAGUS AND STOMACH. The aorta arose in the usual manner from the left ventricle passing upward, behind and to the right of the origin of the pulmonary artery. The aorta then turned posteriorly and slightly to the left. Three centimetres from its origin, in the portion running posteriorly and slightly obliquely to the left, the aorta divided into two. One branch passed to the left of the trachea and œsophagus, the other to the right of these structures. These two divisions united again posterior to the œsophagus and slightly to the left of the mid-line, forming the descending aorta which coursed caudalwards on the left side of the vertebral column in the usual manner. The œsophagus and trachea were thus enclosed in a vascular ring formed by the reduplication in the transverse portion of the arch of the aorta. The right division of the aortic arch gave origin to the right subclavian and right common carotid arteries; the left division gave origin to the same vessels on the left side. The obliterated ductus arteriosus, coming from the pulmonary artery, joined the left branch of the aorta just beyond the subclavian artery.

The measurements were as follows: The circumference of the ascending aorta was 2 cm. The division of the aorta commenced 3 cm. from the aortic valves. The right arch was 1.7 cm. in length, the left was 1.5 cm. The circumference of each of these arches was 1.5 cm.

The arterial ring formed by the reduplication of the transverse aortic arch encircled the œsophagus midway between the pharynx and stomach. Above this level the œsophagus was dilated, having a diameter of 1.5 cm. At the level of the vascular ring the œsophagus was 0.7 cm. in diameter. Below the constriction it gradually increased to a diameter of 2 cm. Where the œsophagus passed through the diaphragm it measured 1.2 cm. in diameter. The cardiac opening in the stomach showed no abnormal constriction. The stomach was small with a capacity of about 1 oz. The walls were comparatively thick due to contraction.

The larynx and upper portion of the trachea were normal. Just above the bifurcation the trachea passed through the arterial ring. At this point it lay directly anterior, and in close apposition, to the œsophagus. These two structures were compressed together by the arterial ring, so that the trachea was flattened in its anteroposterior diameter. The œsophagus was pressing the muscular portion of the trachea forwards, so that the lumen was very small. This compression of the lumen was also present in the proximal portion of the right and left main bronchi.

The recurrent laryngeal nerve on either side hooked around the respective divisions of the aortic arch and passed upwards between the œsophagus and trachea to the larynx.

Culture of the lung grew pneumococcus type 19.

PATHOLOGICAL DIAGNOSIS: (1) Double aortic arch; (2) compression of trachea and œsophagus; (3) bronco-pneumonia (bilateral); (4) otitis media (bilateral).

Comment.—In this patient the vascular circle formed by the double aortic arch was constricting the trachea and œsophagus. There was sufficient continual pressure to cause stridor from birth. A brassy cough developed at two months of age, and may have been due to the relative increased compression of the trachea, or to pressure on, or irritation of, the recurrent laryngeal nerves. With the taking of larger quantities of food this partial occlusion was further emphasized, so that severe attacks of cyanosis were observed. Roentgenograms made to account for this revealed the constriction of the œsophagus, which suggested some anomaly of the aortic arch.

Blackford, Davenport and Bayley[1] presented the first report in English of a case of right aortic arch recognized during life. It was from their report, and from a similar case seen at the Boston Children's Hospital[2], that this type of anomaly was considered in our case.

Through the kindness of Dr. K. D. Blackfan we have the report of the case at the Boston Children's Hospital[2]. The infant presented a history of choking and difficulty in breathing from birth to the time of admission at five months of age. There was no vomiting, but some refusal of food and apparent difficulty in swallowing. The roentgenogram of the œsophagus showed it to be pushed forward at the level of the third and fourth dorsal vertebræ. The infant died of broncho-pneumonia. Post mortem a vascular circle about the trachea and œsophagus was found, which was formed by a right aortic arch that passed above the right bronchus and behind the œsophagus, uniting by the obliterated ductus arteriosus with the pulmonary artery, thus completing the ring.

In the report by Blackford[1] diagrammatic tracings and the original roentgenogram show a displacement of the œsophagus to the left at the level

of the third and fourth dorsal vertebræ, though there were no signs or symptoms of dysphagia or interference with respiration.

Discussion.

In an early stage of the development[3] of the vascular system the ventral aorta is given off from the cephalad portion of the heart, which at that stage has two chambers. This divides into two branches from each of which six aortic arches arise, passing dorsally to the bilateral dorsal aortæ, which as they pass caudad join to form a single trunk. A longitudinal septum develops in the heart, making four chambers, and the pulmonary aorta becomes separated from the ventral aorta. The vascular system lengthens and curves are formed to take up the elongation. The aorta courses to the right from its origin in the left ventricle in this stage. Due to the direction of the stream, the slack produced by the elongation of the vascular system, body curvature and possibly some other mechanical factors, the flow tends to be greater in certain portions, so that some of the arches are more adapted to carry the blood and these enlarge[4] : the others disappear. The fourth left bronchial arch normally becomes the main stream in all mammals, and forms the transverse portion of the arch of fully developed aorta[3, 4]. There is some question regarding the fifth bronchial arch. By some it is believed to unite with the fourth in the formation of the arch of the aorta. The third arch on either side becomes the internal carotid artery. The fourth arch on the right becomes the subclavian artery, and the right primary division of the ventral aorta forms the innominate artery. The left pulmonary artery is joined to the descending aorta by the ductus arteriosus, which is the vestige of the sixth bronchial arch.

In birds, due to mechanical factors acting differently, the tendency of blood flow is not the same. The fourth arch on the right side is maintained and the left atrophies. In reptiles both fourth arches are maintained[3]. Both of these forms of development, which are normal for the species mentioned, are found in humans, the type which is normal for birds occurring much more frequently than the reptilian form. It is the latter type which was found in the case reported here. The development of the aortic arches in the embryo pig and chick are beautifully described by Congdon and Wang[4].

In 1930, Rochdestwenskig[5], searching the literature, collected 12 cases of double aortic arch. Sprong and Cutter[6] collected 15, and also in the same year Lockhart[7] found 19 and adds one of his own.

Lockhart states that most are found in children dying within seven months of age, exhibiting stridor, cyanosis, dysphagia and pulmonary infection. In those that survive to adult life one or other arch is much smaller, usually being only a fibrous band, or barely pervious, and rarely causing symptoms. Rochdestwenskig's patient was, however, a man of 55, in whom symptoms began shortly before death.

Sprong and Cutter, in collecting from the literature 100 cases of the anomalies of the arch of the aorta with the right arch present, found that

simple right aortic arch with variations of vessel origin comprised 39 per cent., double aortic arch 15 per cent. and situs universus the remainder. Poynter[8] found that double aortic arch accounted for 2·2 per cent. of the reported cases of anomaly of the arch of the aorta.

Persisting double aortic arch forms an arterial ring through which certain structures pass. These have been the trachea alone, trachea and

FIG. 3.—Photograph of specimen: anterior view.

œsophagus, and the thoracic duct and pulmonary vessels have been included. Both recurrent laryngeal nerves usually hook around the respective aortic arches[5, 6, 7, 8]. The usual type encloses the trachea and œsophagus. It is believed that the case with the trachea alone may not have been a true double aortic arch, but rather due to some anomalous artery from the arch of the aorta.

Assman[9] described first the diagnosis during life of right aortic arch in 1918. Since then there have been others using his criteria who have made

the diagnosis. Renander[10] found an abnormal kinking of the œsophagus after the giving of barium in a patient with dysphagia, and made the diagnosis. He later reconstructed the anomaly in plaster-of-Paris from his knowledge gained by the roentgen studies. Blackford et al. diagnosed the condition in a child of nine years, who was still alive at the time of the report.

FIG. 4.—Photograph of specimen: posterior view.

The criteria for the diagnosis in all these reports is the finding of a kink in the œsophagus seen with barium by means of roentgen rays. The kink is at the level of the third and fourth dorsal vertebræ, showing a displacement of the œsophagus to the left and forward, then downward, backward, and finally to the right, continuing down to the stomach in line with the upper segment. In none of these was there a vascular circle or a complete double aortic arch. In the case here reported the line of the œsophagus did not deviate from its general direction (Fig. 3 and 4),

The kinking was more of the nature of a constriction at the level of the third and fourth dorsal vertebræ. This, taken with the dysphagia, cough, stridor and choking spells, indicated that there was a constriction of the œsophagus and trachea rather than a deviation due to the right aortic arch or some tumour mass. In the case from the Boston Children's Hospital the vascular arch was completed by the ductus arteriosus and pulmonary artery with a right aortic arch.

Bronchoscopy and œsophagoscopy were to have been attempted in our patient, but due to the respiratory infection this was not carried out. These might have shown a pulsation on all sides at the level of the constriction.

The diagnosis of constriction due to some form of vascular circle can be made clinically. To be more specific, however, and to state the exact type of anomaly, seems to be impossible. This is of importance, for if the anomaly were recognized surgical measures might hold some hope if the exact type were known. In these cases the prognosis is poor when symptoms start early in life[7], and any measure that holds some hope for them is worth while attempting.

In anomalies of the aorta with a vascular circle about the œsophagus and trachea, the œsophagus is constricted rather than deflected to the left. Roentgenologically, this is the distinguishing factor from the simple right aortic arch. This, with the symptoms of constriction of the œsophagus and trachea, make up the picture of vascular circle.

Summary.

A case of double aortic arch with clinical, roentgen and anatomical data is here reported. The difference in the roentgen picture from simple right aortic arch is discussed. A review of the embryology and recent literature is given. A short summary of a similar case from the Boston Children's Hospital is included.

REFERENCES.

1. Blackford, L. M., Davenport, T. F., & Bayley, R. H., *Am. J. Dis. Child.*, Chicago, 1932, XLIV, 823.
2. Blackfan, K. D., *Report from Dr. Blackfan's Clinic, Boston Children's Hospital.*
3. Bailey & Miller, *Textbook of Embryology*, N.Y., 1916, Ed. 3.
4. Congdon, E. D., & Wong, H. W., *Am. J. Anat.*, Philad., 1926, XXXVII, 499.
5. Roschdestwenskig, K. G., *Anat. Anz.*, Jena, 1929-30, LXVIII, 145.
6. Sprong, D. H., & Cutter, N. L., *Anat. Rec.*, Philad., 1930, XLV, 365.
7. Lockhart, R. D., *J. Anat*, Camb., 1929-30, LXIV, 189.
8. Poynter, C. W. M., *Univ. Nebraska Stud.*, Nebraska, 1916, XVI, 229.
9. Assman, H., *Klin Röntgendiag. d. inn. Erkrankungen*, Leipzig, 1924, Ed. 3, 103 (quoted from Ref. 1).
10. Renander, A., *Acta Radiolog.*, Stockholm, 1926, VII, 299.

THE INCIDENCE OF SUGARS IN THE URINE OF INFANTS AND CHILDREN

BY

M. FIKRI, B.Sc., M.B., B.Ch.,

AND

MAH. A. EL-SAYED, M.B., B.Ch.

(From the Pædiatric Department, Faculty of Medicine, Cairo.)

The testing of urines of infants and children for reducing substances is often neglected, owing to difficulties in obtaining specimens of urine, particularly in infants, and to the rarity of diabetes in children.

For the purposes of this investigation, specimens of urine from 150 children, aged 2 months to 5 years, healthy and diseased (other than recognized diabetes), were examined for reducing substances both by Fehling's and Benedict's methods. Three specimens, taken on three successive days, were thus examined, and when a reducing substance was detected, the nature of the sugar was determined by the phenyl-hydrazine test. A sugar tolerance curve was made in the cases which showed the presence of glucose in the urine.

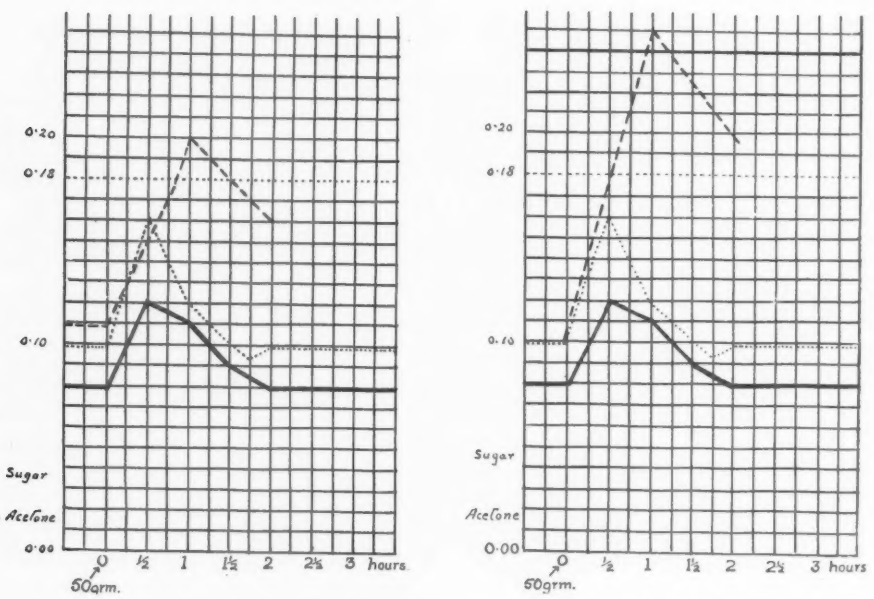
Of the apparently healthy children, numbering 63, one case only, that of a girl 4 months old, breast-fed, showed a reducing substance in the urine, which proved to be lactose. Its appearance was only transient, as succeeding specimens of urine were negative.

Of the diseased children, numbering 87, eleven or 12·5 per cent. showed the presence of a reducing substance in the urine. In all the eleven cases, the reducing substance was lactose, and in three glucose as well was detected in the urine.

Of the eight children who showed lactose only in the urine, five showed the presence of this substance to be only occasional, as succeeding examinations gave negative results. In three instances the excretion of lactose persisted; these were cases of Pott's disease, multiple boils, and pulmonary tuberculosis. The last two were purely breast-fed, the first was fed on the breast as well as animal milk.

The three cases that showed the presence of both lactose and glucose in the urine were of interest. One of them, a girl 8 months old, died on the same day and no sugar tolerance test was done. In the other two cases,

both female infants of 9 and 6 months of age, a sugar tolerance curve was made, on a dose of glucose equal to 1 grm. per kgrm. of body weight given per os. The curves as shown in Fig. 1 and 2 demonstrate the features characteristic of diabetes mellitus. The history of these two infants showed that for some months past, they were wasting with no apparent cause. Both were purely breast-fed. One was admitted with a diagnosis of marasmus of doubtful origin, and died on the fifth day. Post-mortem examination showed broncho-pneumonia in both lungs, but no other lesion of importance. The other case was also admitted with a diagnosis of marasmus and broncho-pneumonia. She also died on the fourth day, and post mortem nothing of importance was found, except the lesions in the lungs.



FIGURES 1 and 2.—Sugar tolerance curves.

..... Normal adult curve.
——— Normal infant curve.
- - - - - - Diabetic infant curve.

Discussion.—(1) Lactose can be passed occasionally in the urine of infants and children, even in health, but more frequently in disease, such as severe disturbances of the digestive tract and infections. It can be distinguished from glucose by the phenyl-hydrazine test, and by the fact that its presence in the urine is usually only occasional.

(2) Glucose when detected in the urine of infants and children is suggestive of diabetes. A sugar-tolerance test will confirm the diagnosis.

(3) Diabetes should be considered as a possible ætiological cause of marasmus in infants.

The normal sugar tolerance curve in infants

For the purposes of the preceding investigation, an attempt was made to determine the characters of the sugar-tolerance curve in infancy and early childhood. The test was carried out on 14 normally developing children, whose ages varied from 5 to 18 months. In each an estimation of the fasting sugar, the maximum rise, the time for that rise to take place and the fall to normal, were determined. The dose of glucose given for the purposes of this test was 1 grm. per kgrm. of body weight, dissolved in a little water. In no case did glucose appear in the urine. Fig. 3 shows the sugar-tolerance curve constructed on the average of figures obtained from this investigation.

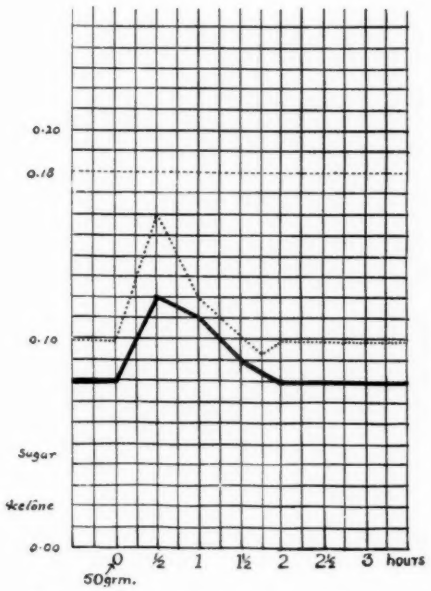


FIG. 3.—Sugar tolerance curve in infants.

..... Normal adult curve.
——— Normal infant curve.

Discussion.—(1) The fasting sugar varied from 0·074 to 0·118, with an average of 0·094 per cent. This figure, perhaps, does not represent the true fasting level because some of the children were being breast-fed before the test.

(2) The average maximum rise was 0·032 per cent., and occurred in the large majority of the cases (in 65 per cent.) in the first half hour.

(3) The time of fall to fasting level was 1½ hours in the large majority of the cases.

(4) The average blood sugar after two hours was 0·081 per cent., which is lower than the original fasting level.

(5) The curve in general points to a condition of increased carbohydrate tolerance.

REFERENCES.

Allen, F. M., *Glycosuria and Diabetes.*
Brown, M. J., *Quart. J. Med.*, Oxford, 1925, XVIII, 175.
Corley, R. C., *J. Biol. Chem.*, Baltimore, 1929, LXXXI, 541.
Fries, M. E., & Kohn, J. L., *Am. J. Med. Sci.*, Philad., 1925, CLXX, 547.
Spence, J. C., *Quart. J. Med.*, Oxford, 1920-21, XIV, 314.
Tisdall, F. F., Drake, T. G. H., & Brown, A., *Am. J. Dis. Child.*, Chicago, 1925, XXX, 829.

INFANTILE SEPSIS AND ITS NUTRITIONAL EFFECTS

BY

A. G. OGILVIE, M.B., B.S., M.R.C.P.

Assistant Physician to the Babies' Hospital, and the Royal Victoria Infirmary, Newcastle-upon-Tyne.

There is a common variety of infantile infection which is characterized by successive septic manifestations, and by well-marked disturbance of health and nutrition. The clinical observation of 31 cases of this affection forms the basis of the present communication. They have all been personally observed, and for this reason have been selected from the large number seen at the Babies' Hospital. No other method of selection has been employed.

Sepsis of the newly-born has been closely studied, and has formed the subject of many articles[10, 15], both in the past, and of recent years; and pædiatric text-books deal with it at some length.

Sepsis in later infancy has claimed but a fraction of this interest. When mentioned, it is briefly described as a rapidly fatal illness, and is regarded, indeed, as an acute pyæmia. Feer[1] thus expresses the prevailing view: 'The outlook generally is bad. In advanced infancy it is not entirely hopeless.'

Such accounts leave a strong impression that they are not based on the observation of cases similar to the majority of those reported here.

It is true that a number of writers (Friedlander[3], Holsclaw[4], Druss[5], Wilson and Schloss[6], Dean[7], Floyd[8], Rogatz[9], Kugelmass and Lampe[13]), and notably Marriott[2], have given valuable accounts of certain septic processes and their general effects in infants. They have all alluded to the frequency of associated sepsis in the cases described. In all instances, however, their writings have been concerned primarily with a particular lesion, such as otitis or pyelo-nephritis, and no account of general sepsis has emerged. It is possible that extreme familiarity with the condition has led to a lack of interest in the study of it. Be this as it may, this 'septic disease of infancy' is an extremely important and often puzzling cause of ill-health amongst the infantile population.

It is not suggested that sepsis in later infancy differs in any vital way from sepsis in the newly born. Indeed, sepsis neonatorum is sometimes quite clearly the starting point of infantile sepsis. Again, in the majority of cases, the first septic manifestation is preceded by a period of ill-health commencing in the neonatal stage.

von Reuss[10], writing of sepsis neonatorum, says:—

> It is quite possible that some disturbance of nutrition or growth at a later period of infancy, apparently due to constitutional weakness, or some marasmic or atrophic state, has its origin in an unknown septic infection of the new-born period, whether it be due to chronic sepsis or to some inferiority and deficient organic resistance resulting from the past infection.

This suggestion is strongly supported by the present series of cases, and when one considers the homes from which most of the cases come, the possibility of an overlooked neonatal infection is readily appreciated. The point will be discussed later.

Generally speaking, sepsis of the newly born is an acute pyæmia, and has been frequently described as such. It is therefore excluded from the present article, though the following qualification is necessary. Not all cases of sepsis neonatorum are acute pyæmias, and this has been recognized by von Reuss, who has given us the best description of this disease. A final quotation from his book, therefore, will form a good introduction to an account of sepsis in older infants :—

> The course of septic infection is extremely multiform. Apart from those violent cases which lead to death within a very short space of time, there are subacute and chronic forms which may last for weeks. Sometimes the disease pursues its course in the most alarming manner, with high fever and all the described general symptoms; in other cases the form of disease is so indefinite that one may finally be in doubt whether a general infection is actually present, or merely general constitutional weakness, the condition resulting from underfeeding, or the onset of nutritional disturbance.

Ætiological factors.—Infancy is here understood to refer to the first two years of life; as far as reaction to infection is concerned, the third year seems to belong rather to early childhood than to infancy.

Of the 31 infants in the present series, 19 were boys and 12 were girls. Prematurity was not an important factor : only three of the children were prematurely born. One child was a full-term twin, and one other was said to be weakly at birth, but with these exceptions it may be taken for granted that the infants were healthy when born. This point has been investigated with some care.

As far as could be ascertained, confinement and puerperium were uneventful in all cases. A definite history of sepsis in the neonatal period was obtained in four cases only, but it must be emphasized that this apparent freedom from neonatal infection cannot be accepted without question. With two exceptions, the babies came from poor homes, in which exposure to septic infection was likely to be frequent, and its occurrence in any but a severe form likely to be overlooked or forgotten. The majority were members of families of more than four children, living in one, two, or at most three rooms, and poverty and overcrowding cannot be disregarded as important pre-disposing factors.

Only seven of the children had been breast-fed for longer than 10 days. Tuberculosis and syphilis were of no importance as predisposing causes.

A study of the clinical records suggests a division of the cases into two groups, acute and subacute, according to the mode of onset and the course of the illness, and they are therefore considered in this way. It will be seen that the acute cases are reminiscent of sepsis neonatorum, though the prognosis is much better; whereas the subacute cases have rather a different history.

Acute infantile sepsis.—A healthy, thriving infant suddenly becomes acutely ill; he is, as the Northumbrian mother expresses it, ' dead felled.' If at the same time, or within a few days, an examination of the urine reveals the presence of pus cells in quantity, or should cough, cyanosis and dyspnœa be prominent symptoms, the diagnosis may be easily made. Often, however, more or less severe vomiting, accompanied perhaps by a green, watery diarrhœa, suggests some digestive disturbance which yet seems inadequate to explain the rapid loss of weight and strength which follows; or there is no obvious sign or symptom to indicate the cause of this sudden and even alarming change in the infant's condition. The patient may improve slightly, but remains unhappy, fretful, and underweight. His expression is anxious, he cries hungrily and yet refuses everything that is offered to him except water, of which he takes greedily. He is pallid and wasted, with more or less diminution of subcutaneous fat, and evidence of dehydration. His muscles are weak and flabby, and a varying degree of anæmia is present, as is shown by a hæmoglobin percentage of 50, 60 or 70. No change is noticed for a week or two, it may be; vomiting and diarrhœa subside or become less pronounced, and little further wasting occurs. Then two to six weeks after the onset, an acute exacerbation of symptoms takes place, with fever, and the appearance of a profuse aural discharge, or perhaps the discovery of pus in the urine, enables a diagnosis to be made. As this disturbance subsides the patient's general condition improves, and he may appear to be convalescent. His weight rises, his appetite returns to normal, and he becomes relatively happy and contented.

This appearance of recovery is, however, frequently illusory. A few weeks later, often before the previous lesion has completely healed, a recurrence of acute symptoms heralds a second septic manifestation: extensive skin sepsis, perhaps, or broncho-pneumonia.

Final recovery may now take place, but further sepsis frequently follows. The infant may suffer from four or five successive septic lesions before his disease comes to an end. Though any of these may prove fatal, the outlook is a favourable one, provided that recovery in the intervals is good, no matter how alarming the exacerbations may be.

Unhappily, by no means all the cases follow this course. In certain others, instead of a degree of recovery in the intervals, there is a steady and often rapid deterioration. The weight falls, the digestive and other symptoms persist or become aggravated, and the child takes less and less interest in his surroundings. The intervals between one septic manifesta-

tion and another are short, and no attempt at healing is made; the course of the disease is steadily downhill with little or no sign of improvement at any time, and the resemblance to sepsis neonatorum is close.

Six of the twelve cases in this group were of this severe type and all died, the average duration of the illness being eight weeks. Of the remaining six cases, who corresponded to the description given above, only one died. The average duration of these cases was twelve weeks.

Subacute infantile sepsis.—The onset in these cases is insidious, and is in well-marked contrast to the dramatic commencement in the acute group. There is a history of a prolonged period of vague ill-health of from 6 weeks up to 9 months, and followed by the appearance of an obvious septic lesion. In most cases this history dates from the first few weeks of life, but in some the infant thrives for some months, and then gradually 'goes back.' He becomes listless and unhappy, his appetite fails or is capricious and variable, irregular vomiting or diarrhœa perhaps occurs, he ceases to gain weight or slowly wastes, and his muscles become increasingly weak and flabby. His complexion may be noticed to assume a sallow, earthy tinge, and a slowly developing pallor of the mucous membranes and of the palms of the hands suggests a progressive anæmia, which is confirmed by finding a hæmoglobin percentage of 60, 50 or 40.

The appearance of the patient may be suggestive of a chronic infection, but in the first weeks or months of the illness the impression often gained is that of a badly nourished or unsuitably fed baby, or of some nutritional disorder. This impression is often strengthened by the appearance and circumstances of the mother, by her account of the infant's diet, and by the appearance of rickets in other members of the family, if not in the patient himself. She states that no food suits the child, and it is found on enquiry that frequent changes, and irregularity in feeding, have been the rule. The diet, in short, has been 'everything by starts, and nothing long.' If, however, the child is taken into hospital and placed on an adequate and carefully balanced diet, with anti-rachitic treatment should this appear to be advisable, the result is disappointing. The weight may rise a little at first, but the general trend is downward; the appetite does not improve, and recurrent attacks of diarrhœa and vomiting may cause doubt and difficulty in feeding. Anæmia is progressive, and the patient seems to become weaker and flabbier, in spite of all the care that may be taken.

At length, a more pronounced rise of temperature with evidence of general febrile disturbance indicates some fresh development, and in a day or so definite evidence of this is found : and a pustular eruption, or a nasal or aural discharge, perhaps, shows the septic nature of the illness. The lesions of subacute infantile sepsis are slow to heal, but the more acute symptoms of exacerbation subside fairly quickly, and some slight degree of general improvement may take place. Generally speaking, however, the infant's condition remains stationary. As in acute sepsis, successive septic

manifestations occur, but the degree of recovery is much less in the intervals, and the intervals themselves tend to be longer. An interesting feature is the occurrence of symptoms suggestive of an exacerbation without corresponding change in local signs, or the appearance of any fresh infective focus. There may be fever and toxæmia, an attack of diarrhœa and vomiting, or a mere loss of appetite accompanied by a well-marked fall in weight.

Final improvement commences as insidiously as the disease itself, and continues unchecked by further sepsis. It is not uncommon for skin sepsis or pyuria to occur or recur at this time, but no check in the general improvement is noted, and the lesions heal rapidly. It would appear that a point is reached at which the infant acquires sufficient resistance to enable him to kill his infection.

An improved appetite is usually the first sign of recovery, and this is accompanied by an increased power of digestion. The child's food now seems to do him good, and he gains weight and strength steadily. The anæmia, unaffected by iron medication, now undergoes spontaneous cure, and the patient, who before lay listless in his cot, or sat with his legs crossed, looking tired and bored, shows a new interest in his surroundings and an evident desire to move about. In six or eight weeks he is fit for discharge.

The average duration of the disease in the 19 cases was seven months, although one case ran a course of nearly two years before final recovery took place.

With regard to prognosis, it may be said that the mortality rate in the subacute cases was half that in the acute, and that the more protracted the illness the better the chance of recovery. Six of the nineteen cases died, and their average duration was under five months. The average duration of the 13 cases which recovered, on the other hand, was over nine months.

Recovery, when it has occurred, has been practically complete. All these children have been followed for over two years, and all have remained well, though such a condition as pulmonary fibrosis, which followed pneumonia in a few cases, still gave evidence of its presence, as indeed might be expected.

Discussion.

The importance of this disease lies in the frequency with which it occurs, the amount of severe illness in babies for which it is responsible, and the serious difficulties of diagnosis and prognosis to which it may give rise.

The influence of sepsis on the general infantile mortality rate is uncertain, as this diagnosis is not accepted by the Registrar-General. It must, however, be not inconsiderable. Again, septic infection is a serious problem from the institutional point of view. The prevention of ward infection is an ever-present consideration in any institution where infants

are collected together for purposes of treatment, and infantile sepsis as a cause of ward infections stands alone. The nursing of a septic infant requires special precautions, and the indefinite character of the symptoms during certain phases of the disease is an added difficulty. Many cases which would formerly have been regarded as 'feeding' cases are now recognized as cases of infection, and every patient in the Babies' Hospital is regarded as a potential source of infection, and is placed on infectious precautions. Definitely 'clean' cases, such as those of pyloric stenosis, are nursed in special rooms, but the same precautions are observed as an additional protection for them.

The frequency of the disease is shown by the following analysis of the cases admitted to the Babies' Hospital since 1922. In all probability it is under-estimated, as in the earlier years the diagnosis was less likely to be made.

Sepsis	180
Digestive and nutritional	182
Bronchitis and pneumonia (all kinds) ...	132
Pyloric stenosis	121
Tuberculosis	108
Rickets	108
Gastro-enteritis	71
Congenital defects	68
Pink disease	45
Prematurity	37
Other conditions	142

Clinical features.—Clinically the most important feature of the disease is the indefinite nature of the general symptoms, and their variability. They vary from persistent misery and fretfulness, or mere failure to thrive, to recurrent attacks of diarrhœa and vomiting which may be severe and alarming. As an example the following case may be reported :—

Case 1.—Male, aged 6 months. He was healthy when born, though a twin, but had never thrived since the second week, when he had a septic rash. He was always unhappy and continually crying, difficult to feed, and liable to occasional attacks of diarrhœa and vomiting for no apparent reason. He remained persistently underweight, alternately gaining and losing. When first seen he was puny and anæmic, with small, flabby muscles and a perpetual whining cry. His weight at 6 months was only 9 lb. 10 oz. General examination revealed little else. The father was an unemployed miner, and malnutrition due to social conditions might appear to be a likely diagnosis. The tuberculin test was negative. On the fourth day after admission, however, pus cells in large numbers were found in the urine. (It may perhaps be observed, in passing, that for the early diagnosis and proper observation of renal sepsis in babies, the microscopical examination of daily specimens of urine is essential: pyuria in them shows wide fluctuations, is intermittent, and is readily overlooked.) The hæmoglobin percentage (Sahli) was 60, the leucocytes numbered 21,000 per c.mm., and a differential percentage count resulted as follows: Polymorphonuclear, 34; lymphocytes, 51; monocytes, 10; meta-myelocytes, 3; eosinophils, 2. Slow improvement took place, and this was steadily maintained throughout the child's stay in hospital. The pyuria cleared in a fortnight, to recur 10 days later, coincident with a very slight check in the general progress. Skin sepsis

supervened, but both lesions rapidly and finally healed, and he was discharged two months after admission. Cure was evidently complete, and when seen four-and-a-half years later he was well and active, and had remained in good health since discharge.

What view are we to take of this illness? Are we to regard it as a pure nutritional disorder, complicated at the age of 6 months by an infection; or as an infection of long standing, giving rise to marasmic and dyspeptic symptoms?

That nutritional disorder is an important factor in the production of infantile illness is not in dispute, and the circumstances of this child's home were favourable for the production of such disorder, as has been stated.

Closer consideration of the whole history, however, suggests a different view. At the age of 2 weeks this infant had a 'septic rash' over its body. It is, of course, open to us to question the nature of this. But whatever it was, it is clear that before this time the child was healthy and thriving, and that afterwards, up to the time of admission, he was ailing. The rash, even if non-infective itself, may easily have been evidence of the fact of infection. Septic infection is easily overlooked in a working-class home, but nearly every mother notices when her child is fretful or unhappy, or manifestly compares unfavourably with the children of her neighbours in his rate of progress. Even should she not, her neighbours will themselves eagerly point this out to her. The whole course of the disease in hospital strongly suggests that this period was actually the terminal recovery stage of an infection which had already existed for some time previous to admission. The weight and temperature charts, and the persistence of normal stools throughout, are all opposed to the idea of an acute septic infection occurring in a case of severe nutritional disorder. The steady gain in weight is not what would be expected in the case of a grossly under-nourished child attacked by an acute septic infection: it is surely more suggestive of a highly resistant patient steadily overcoming his disease. It is quite probable that had the baby been born into a home further above the poverty line, he would have recovered more quickly: but this consideration cannot weaken the argument.

This case has been quoted and discussed at length as illustrative of what is considered to be an essential feature of the disease. Further examples, in which the whole or the greater part of the illness has been observed in hospital, could be quoted to support this view, but have been excluded to avoid repetition.

As illustrating the ease with which septic manifestations can be overlooked; the following may be briefly quoted:—

Case 2.—A female infant, aged 10 weeks, was admitted with a history of violent diarrhœa and vomiting for two days. The symptoms were due to severe renal sepsis, from which the child died 10 days after admission. On examination at the time of entry into hospital, however, a perforation of the right ear drum was noted, and although there was no obvious discharge externally, pus was oozing through the perforation and was present in the middle ear. Careful questioning could not elicit the statement that discharge from the ear had been noticed at any time, and it must be assumed that little

obvious discharge had ever been present. The fact of infection was, however, indisputable, and the conclusion that the otitis was the primary lesion, and hence the source of the fatal pyelo-nephritis, is difficult to avoid.

Disorders of nutrition are widely discussed at the present time, and have stimulated much valuable original work. Nutritional anæmia, in particular, which has for so long been neglected in this country, is now being placed on a sure footing by Mackay and Parsons. Vitamin and mineral deficiencies, quite rightly, have occupied, and still occupy, much space in medical literature, and the subject of infant feeding has claimed a large amount of medical attention. That such subjects rightly take such an important place is too obvious for argument, but it nevertheless seems quite possible that the rôle of infection, and especially septic infection, may be seriously under-estimated. ' Dyspepsia ' and ' marasmus ' are unsatisfying terms as final diagnoses, and careful and persistent search for infective lesions, especially septic lesions, should be made before these or similar labels are applied.

Portal of entry of the infection.—It will be gathered from the foregoing remarks, that the exact mode of entry of the infection may be impossible to determine with any certainty. The first known lesion may not be the true primary focus.

The recognition of this difficulty is implied in the varying views which are held as to the most frequent sites of primary septic foci in medical literature. Marriott[2], for instance, in a series of papers, has strongly expressed the view that aural septic infection is one of the most potent causes of infantile alimentary disorder; and the observation of cases such as those described above certainly gives some support to this view, though hardly encouraging one to go as far as he does in this direction. The extreme importance attached to the ear as the primary focus, also, seems exaggerated. Druss[5] argues against this view, basing his argument on the chronology of the symptoms and the frequency of post-mortem aural changes in normal subjects. He believes that the bowel is the portal of entry in such cases. Others support Marriott's view (Holsclaw et al.[4], Dean[7], Floyd[8], Hartman[11], Preysing[12]).

The matter is indeed impossible of proof at present, because insufficient is known of generalized infantile sepsis. Until careful pathological and bacteriological studies have been made on a sufficient number of cases, the matter can go no further than argument.

A survey of 180 septic cases admitted to the Babies' Hospital indicates that the respiratory route appears to have been greatly under-estimated as a mode of infection in infants, and that the skin and the mouth are frequent sources of septic infection, as they are in sepsis of the newborn. The figures are small, however, and afford no proof.

The source of infection has not been determined in the great majority of cases. In neonatal sepsis this is much easier to trace, and yet cryptogenetic cases are frequent. When first seen months after the primary infection, the problem is usually insoluble, and persistent enquiry has failed to provide an answer in the present series. Septic infection in the

attendants seems a most probable explanation, but the possible contacts in the homes of the poor are legion.

Maintenance of the infection.—An infection which persists and exerts its influence for so long a time, suggests by analogy with other chronic infective diseases, that it is maintained in some nidus within the body, and acts by producing general toxic effects and local metastases. Such a focus of infection, conveniently referred to as the ' basal lesion,' will vary in activity with the resistance of the tissues of the host and other factors, like any infection. At one time it may produce mild dyspeptic or nutritional disturbance, and at another may become locally virulent; or it may invade the blood stream temporarily, thus giving rise to embolic sepsis.

This basal lesion could be identified in a number of the cases, though in others this was impossible. The latter are thus truly ' cryptogenetic,' and must remain so until more pathological knowledge of the disease is available. It seems likely, however, that in these cases also a basal lesion was present, though not certainly identified.

The fear of arousing a sense of tedium in the reader has led to a severe restriction of the number of cases quoted in any detail, but two illustrations may be given here:—

Case 3.—A boy, aged 5 months, was admitted because of failure to thrive. Born healthy, some vague upset at the end of the second week had been followed by persistent, though irregular, vomiting, with intermittent diarrhœa, and failure to gain weight. On admission some bronchitis was present, but the general impression gained was that of malnutrition and neglect. A week after admission an acute febrile disturbance preceded the obvious occurrence of aural sepsis on the right side. The discharge varied in amount, but final healing did not take place until three months later. During this time repeated crops of pustules and successive skin abscesses continued to appear, and tonsillitis and septic rhinitis als occurred. Final healing of the ear was promptly followed by rapid and permanent disappearance of the skin sepsis, and final recovery.

Case 4.—A male infant was admitted at the age of 7 months with the history that he had thrived well until he had had broncho-pneumonia at the age of 3 months. Since then he had suffered from persistent cough and had failed to gain. He had not been well for 4 months, according to the mother, and indeed, on admission, weighed only 8 lb. 13 oz. at 7 months. There was marked impairment of percussion note over the left lower lobe and the breath sounds were almost absent over this area. There was a bullous impetigo over the trunk, also, which had been present for a few days. The chest was explored on several occasions with a negative result, although a leucocyte count of over 21,000 indicated an active infection. X-ray examination of the chest showed a marked shadow in the left lower lobe overlapping the heart shadow. The tuberculin reaction was negative. These clinical and radiological signs were slow to clear, and until they did so recurrent skin sepsis was very troublesome. Final disappearance of both signs and X-ray shadow were followed, as in the case just quoted, by rapid and complete healing of the skin infection, and by permanent recovery. Two years later this boy was in good health.

But little comment is required. Both cases point in a suggestive manner to a ' basal ' focus as the origin of secondary infection which permanently healed as soon as this cleared up.

This basal lesion is not necessarily the primary lesion, though often it is so.

Summary.

Thirty-one cases of septic infection in infants have been studied. Infantile sepsis is an important cause of ill-health and death among babies, and is a potent source of institutional infection.

Like any other disease, the prognosis varies as the resistance of the patient and the size and virulence of the infective dose, but it may be said that subacute cases do much better than acute cases; and that the longer a child survives, the greater its chance of ultimate recovery. The general mortality appears to be about 30 per cent. The portal of entry is perhaps most frequently the respiratory tract, although definite conclusions have not been attempted.

The impression gained is that of some basal septic focus, which produces general toxic symptoms and periodic embolic lesions until such time as the patient acquires sufficient resistance to kill the infection, or until death occurs.

No mention has been made of the pathology and bacteriology of the disease, owing to insufficient data. With regard to the hæmatology, Dr. P. Klenerman is at present studying this aspect at the Babies' Hospital, and her results may be published in the near future.

Finally, emphasis has been laid throughout on the pronounced effect of this affection on the digestive processes and the general nutrition, and on the difficulty in diagnosis to which this may give rise. It has long been recognized that severe digestive and nutritional effects are produced by septic infection in infants, but there has been insufficient recognition in the literature of the insidious character often assumed by the disease, and of the ease with which the cause may be overlooked, in spite of the work of Marriott and his colleagues. Clinically, this is much the most important feature.

REFERENCES.

1. Feer, E., *Textbook of Pediatrics* (Trans.), Philad., 1922, 719.
2. Marriott, W. M., *Laryngoscope*, St. Louis, 1925, XXXV, 592, *Am. J. Dis. Child.*, Chicago, 1925, XXX, 577.
3. Friedlander, A. *Acta Pædiat.*, Stockholm, 1927, VI, 433.
4. Holsclaw, F. M., et al., *Am. J. Dis. Child.*, Chicago, 1930, XXXIX, 746.
5. Druss, J. G., *Ibid.*, 1932, LXIII, 356.
6. Wilson, J. L., & Schloss, O. M., *Ibid.*, 1929, XXXVIII, 227.
7. Dean, L. W., *Arch. Otolaryng.*, Chicago, 1927, VI, 201.
8. Floyd, M. L., *Ibid.*, 1925, I, 411.
9. Rogatz, J. L., *Am. J. Dis. Child.*, Chicago, 1930, XL, 70.
10. von Reuss, A. R., *Diseases of the Newborn*, London, 1921, 539.
11. Hartman, *Ztschr. f. Ohrenk.*, 1898, XXXIV, 1.
12. Preysing, *Otitis media der Sauglinge*, Weisbaden, 1904.
13. Kugelmass, N., & Lampe, M., *Am. J. Dis. Child.*, Chicago, 1932, XLIII, 291.
14. Byfield, N., *Abt's Pediatrics*, Philad., 1924, III, 786.
15. Cameron, H. C., *Lancet*, Lond., 1929, i, 1127.

A NUTRITIONAL DISEASE OF CHILDHOOD ASSOCIATED WITH A MAIZE DIET

BY

CICELY D. WILLIAMS, B.M.
(From the Children's Hospital, Accra, Gold Coast Colony).

There is a well-marked syndrome, not uncommonly found among the children of the Gold Coast Colony, which I have not found described. About twenty cases have been seen in the last year.

The syndrome consists of œdema, chiefly of the hands and feet, followed by wasting; diarrhœa; irritability; sores, chiefly of the mucous membranes; and desquamation of areas of the skin in a manner and distribution which is constant and unique.

The disease attacks children of either sex, between one and four years old. It appears to be due to some dietetic deficiency and to be uniformly fatal unless treated early.

In all the cases seen there was a history of an abnormal diet. Breast feeding had been given by an old or else a pregnant woman, and the only supplementary food consisted of preparations of maize, namely arkasa and kenki, as described below.

Family customs.—In order to appreciate the salient points in the patients' history it is necessary to understand some of the local customs of the Gold Coast Colony.

African women lactate far more than European. They breast-feed one child until the next is born, and the deposed baby is still nursed sometimes. It is rare to find an interval of less than two years between each pregnancy. The baby is, therefore, old enough to demand a varied diet—oddments from his mother's stews, vegetables, and fruit—before she becomes pregnant again. The children may be given occasional breast-feeds up to six years old and more. Not only the mother, but the grandmother, aunts, or other women living in the compound will nurse a child, not as a routine, but as a soporific in moments of stress. Some mammary secretion may be present in quite old women who have not had a child for twenty years. The grandmothers are willing to act as comforters even when there is no secretion present.

If a woman dies in child-birth or soon after, the surviving baby is generally adopted by the maternal grandmother, and breast-fed by her possibly with the help of her sisters and other daughters. The women of a family often live in a compound together, so the arrangement is simple.

These foster-children generally die early. It is not a question of the survival of the fittest, but the survival of just a few of the luckiest. In former days, an infant that survived its mother was looked upon by the Ashanti people as a bad ' ju-ju,' and was invariably destroyed. Among the Ga and Fanti and coast tribes this is not so, but they believe that the spirit of the dead mother comes and poisons the child's food, and finally persuades the spirit of the child to follow hers.

It often happens that a child is brought to the clinic, but the medical officer is not informed that the child is motherless. The fact may be simply ignored by members of a coast tribe, or deliberately denied by an Ashanti.

To obtain a family history a very patient investigation is necessary, questions having to be repeated in two, and sometimes three, languages. With many patients to be seen, it is sometimes only by good fortune that important points in a history are discovered.

Diet.—Maize enters largely into the diet of all classes. The two forms in which it is most commonly used are called arkasa and kenki.

Arkasa is universally employed as a food for infants and invalids. It is used as a nourishing drink as we would use coffee or cocoa. In ' Gold Coast Food,' by Miss M. I. Field, the preparation is described as follows :— ' Soured corn-dough is mixed with water in a basin to a smooth paste, and then rubbed through a sieve into a pot so that no husks appear. More water and salt are added and the whole boiled for fifteen minutes. Sugar is often added at the end. The finished arkasa is a rather thick gruel.'

The ' corn dough ' is prepared by grinding white maize, damping it, and leaving it to stand. The sour arkasa is made from corn that has been standing several days, and in which much acetic fermentation has taken place. It is often responsible for gastro-enteritis in children. The sweet arkasa is like a pap made with cornflour, and is an excellent food for children, but not by itself.

Kenki is a staple article of diet for all the coast tribes, and at all ages. To quote the same authority, it is ' corn soaked in water for three days. It is then ground on a stone, sprinkled with water, put into a pot covered with plantain leaves, and left for three days to sour. It is then ground until quite smooth; then the lump is divided into two, and one half is put into a pot of boiling water and stirred for some minutes, till thoroughly mixed with the water. The pot is taken from the fire and the uncooked half is mixed with the cooked half, and the lumps are smoothed out. The mixture is then rolled in plantain leaves or in corn trash and boiled in water for some hours.'

Arkasa, therefore, by itself or with kenki, is not likely to prove an adequate diet. It must be borne in mind, too, that white maize lacks carotene, as well as being, like red maize, deficient in tryptophane, lysine, and glycine.

The diet of the average man or woman consists mainly of kenki and other bulky carbohydrates—yams, cassava or cocoa-yams, boiled or roasted

or beaten into a sort of purée called a ' fu-fu.' This is taken with some dried fish or a stew made of meat, tomato, onions, okra, egg-plant or beans, highly seasoned with the most fiery of peppers. Meat of goats, sheep and chickens is used only in small quantities. Beef is used seldom and only in the towns. Butter is unknown except from tins. Fats are provided mainly from palm oil, palm-kernel, cocoa-nut oil and ground-nuts. Milk, apart from human milk, is not used as an article of diet. The numerous goats are never milked. Tinned milk of good brands, especially the sweetened condensed variety, is on sale in many of the villages. It has been used as a luxury for adult consumption. It is the object of the child welfare workers to have it regarded as a necessary adjunct to the children's diet. Eggs are generally only eaten when hard-boiled. As a whole, animal fats are conspicuously lacking. Fruit is eaten, but not regularly. Bananas, oranges, pineapples, paw-paws and sugar-cane can be had during most of the year; mangoes, and avocado pears in season. Tomatos, egg-plant, okra and onions are widely grown and appear in every soup or stew.

It would not be surprising, therefore, if some of the babies, though apparently healthy at birth, were lacking in some essential factors, especially those contained in proteins and animal fats. This defect perhaps only becomes obvious when there is an extra demand on the reserve stores.

History.—The history of the patients who suffer from the disease I am describing is invariably connected with improper feeding. The mother is dead and the patient has been breast-fed by a grandmother or an aunt; or the mother has become pregnant again while the patient is still young; or the mother has been ill or under-nourished. Always the story is the same—supplementary feeds have consisted of nothing but arkasa, or arkasa and kenki.

Symptoms.—This defective feeding has gone on for four to twelve months, and the patient has developed normally. Then he begins to get irritable; there are attacks of diarrhœa; and swelling of the hands and feet. At the end of a week to ten days the skin changes set in. If untreated, the child dies, generally within a month of the onset of the skin changes.

These changes must be described in detail. In the first place it should be remembered that an African child who suffers from a chronic disease generally shows some degree of depigmentation. This is more marked in diseases with accompanying anæmia, and is particularly conspicuous in a profound helminthiasis. A child who in health would be a rich black or a dark glossy brown, becomes gradually a dull, reddish, muddy colour. With a little experience this colour is easily distinguished from that of a child of mixed race, or that of the tribes who are naturally reddish rather than black, for instance the Fulanis, by the quality of the colour, the texture of the skin and the gloss on its surface. In the condition now under discussion, a mild degree of depigmentation takes place. The hair also in

such a disease as a profound helminthiasis becomes dry, pale, and sparse. These changes may take place to a mild degree in this disease. There is no dryness of the skin, no branny desquamation as is described in pellagra. The changes of skin and hair are more noticeable when the disease is seen in an older child, say of four years, in whom the condition may have become chronic; or perhaps owing to occasional improvements in the diet the child has had a series of relapses and recoveries.

The early picture, then, is one of a child of about eighteen months old, well nourished but irritable, with slight œdema of the hands and feet, and the skin showing some degree of depigmentation. There suddenly appear on the ankles, on the knees, above the wrists, and on the elbows, some small black patches, first on the extensor surfaces and gradually spreading. These patches appear to consist of the epidermis which has become dark, thickened and crumpled, though it remains soft and pliable. The number and extent of these patches increase. Their distribution and their character remain distinct from the rash that is typical of pellagra. Soon the legs and forearms, knees and elbows, are covered with a sort of crazy pavement of this thickened epidermis. In a few days as the older patches mature, they strip off very readily, leaving a pink, raw surface exposed underneath. The œdema subsides at this stage. The patches of desquamation progress up the thigh and may become severe on the buttocks. Very small patches may also be seen on the face, back, and elsewhere.

The appearance of the skin condition at this stage is striking. There is the dark or reddish brown of the unaffected skin, the black patches of crumpled and thickened epidermis, and the raw areas where these have peeled off.

The skin at the corners of the mouth and eyes also begins to peel off, leaving raw areas. There is photophobia, but no eversion of the eyelid as described in the A and B deficiency of Sierra Leone.

By this time the child is in a miserable condition with sores on the mucous membranes, and perhaps a corneal ulcer. Conjunctivitis has not been marked; there has been no dryness of the cornea nor any condition resembling Bitot's spots. The child is extremely irritable, and may die in a few days if it is not treated. It appears that unless the diet is changed before the skin condition is fully developed it is impossible to save the child's life.

It may be noted that the blackened patches on the skin appear first where there is any focus of irritation or pressure. The areas round the ankles, below the knees, and above the wrists are probably determined by the strings of beads invariably worn in these positions. Over the knees, elbows, and buttocks are normal pressure points in a child who is beginning to crawl.

The irritability of these children is always great. There may also be some photophobia, but there is no alteration in any of the reflexes. Diarrhœa is persistent, especially in the later stages. The pulse is rapid,

becoming more so as death approaches. There is an irregular type of pyrexia, which in some cases was modified by a concurrent malaria.

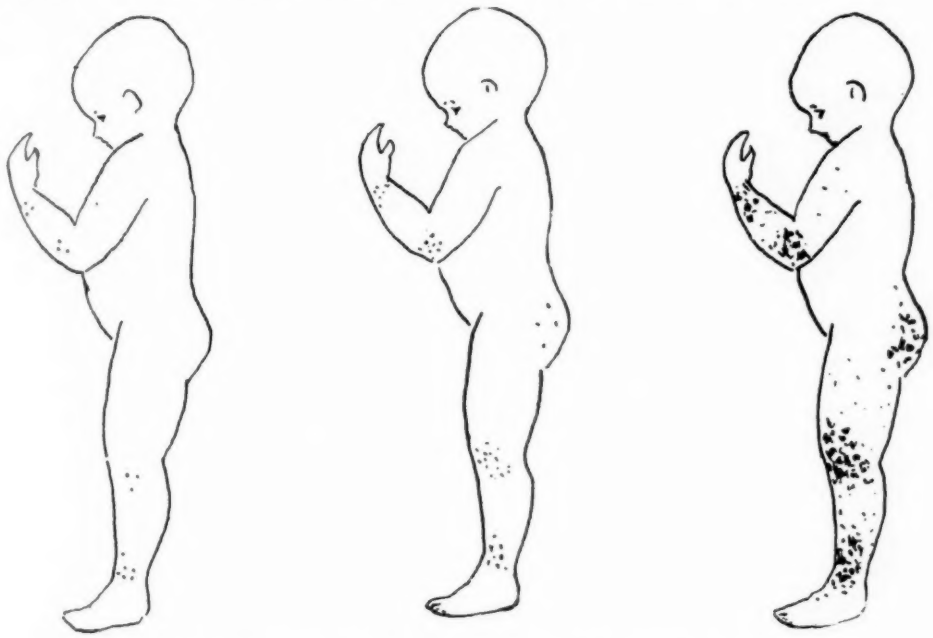


FIG. 1-3.—Showing the first appearance and spread of the rash.

Morbid anatomy.—Three post-mortem examinations have been held. All three have been exactly like that quoted at length in Case 2, the only thing of note being a pale, fatty, almost diffluent liver.

Case records.—Five cases are given in detail. These are chosen largely because the picture was not confused by any accompanying disease.

Case 1.—Female. Her mother, a primipara, had died four days after the birth of the child. Baby was fed entirely by the grandmother, whose youngest child was said to be 2 years old at the time. The grandmother, however, looked at least 60, and her youngest child was more likely to be 12.

She was brought to the children's hospital fairly regularly. The fact that she was motherless was not divulged, and no special instructions were given about the feeding. She suffered from some minor ailments such as bronchitis and malaria, and she was small for her age, but until thirteen months old she grew steadily and gained weight. She then began to lose weight and showed sore mouth, acid saliva, cough, fever, swelling of feet, and intertrigo. Bowels open two or three times a day. Cod-liver oil and malt with quinine and iron, and a mouth wash, were given on July 7th. The Wassermann reaction was negative on two occasions.

The child was brought again on July 14th. She had been so peevish that the grandmother did not get her to take the medicine regularly, and the condition was now well developed. There was much œdema of the face, hands and feet. Unlike the œdema from ascaris, the cheeks were not pendulous, but there was a general puffiness all over the face. Nor was there that bulging of the eyelids so characteristic of nephritis. The tears and saliva appeared to irritate the skin, which was peeling off round the corners of the mouth and the eyes,

The saliva was acid, there were sores in the mouth. The tears were neutral to litmus paper. The child was irritable, but all the reflexes were normal. The skin all over was atrophic in appearance; there were darker, almost pavemented patches on the forearms and the legs. The typical distribution of pellagra was absent:—the dorsum of the hands and feet seemed to escape until the last stages of the disease. The liver was enlarged, and so was the spleen. There was slight anæmia, but the blood count did not show any great abnormality. Nothing pathological was found in the stools or urine. The temperature was irregular at first, but after systematic quinine this settled down, in spite of the fact that no malarial parasites were found in the blood at this stage. In fact, except for the extraordinary condition of the skin, there were no well-marked signs or symptoms.

The dark patches on the skin became more extensive and definite; on the buttocks and other exposed parts the skin rubbed off very easily, leaving large raw areas, indolent, and healing slowly if at all.

It was difficult to examine the child's eyes on account of the irritable condition, and the fact that the gentlest handling was apt to remove large pieces of skin. After about one week the left cornea ulcerated and the eye was destroyed.

The following treatment was adopted: Iodide of iron, calcium lactate, thyroid extract, stovarsol, grey powder, and a mouth wash of sodium bicarbonate. For diet, were given: Lactogen, arkasa, eggs, paw-paw, oranges, bananas, meat-juice.

The child was in hospital for two months, and though she appeared to improve a little, the disease was never arrested.

She died on September 9th of a terminal broncho-pneumonia.

At post-mortem examination nothing definitely abnormal was found except a pale, fatty, almost diffluent liver.

Case 2.—Male microcephalic child, aged 2 years old at death.

The mother was about 14 years old when the child was born. The parents realized that the child was abnormal and neglected it. It was not brought to the hospital until 2 years old, and moribund with this disease. The parents said it was breast-fed entirely up to 18 months. The mother then became pregnant. The child was weaned and fed with arkasa only for the last two months.

The syndrome was well marked. The skin was peeling off fore-arms and legs. Liver and spleen were not palpable. The child died four days after admission.

The photograph, (Fig. 4) was taken after death.

The post-mortem report is as follows: The body was that of an ill-nourished child with a small head. Thorax, lungs and heart normal. Liver enlarged (weight, 560 grm.), pale and firm: cut surface greasy, and blood oozed from the central veins. Gall-bladder full of bile. Spleen congested. Kidneys pale: showed differentiation between cortex and medulla: capsule strips easily. Intestine: extremely thin walled; Peyer's patches prominent; contained green slimy stool.

Culture of intestinal contents; no non-lactose fermenters isolated.

Microscopic section of liver showed marked fatty degeneration.

Cause of death: ? avitaminosis.

Case 3.—Male, first seen March 29th, 1932, aged 14 months. The mother is seven months pregnant. The child was weaned four months ago; since then it has been given nothing but arkasa and kenki. It was in poor condition, with stomatitis, swelling of feet and some areas of thickened epidermis on the back.

Treatment: Cod-liver oil and malt, quinine and iron, with potassium chlorate and boro-glycerine for the mouth. Advised diet containing fruit and eggs and tinned milk.

This treatment was not carried out, and the child was admitted two weeks later with the skin condition perfectly demonstrated. He was exceedingly peevish, with sore mouth, enlarged liver, and some œdema.

No parasites were found in the blood. Stools were loose, but showed no ova or protozoa. There was a trace of albumin in the urine. W.R. (mother and child) negative.

FIG. 4.—Photograph of Case 2, taken after death.

FIG. 5.—Photograph of Case 3, taken three days before death.

Treatment: olive oil to the skin; cod-liver oil and malt, and quinine and iron, with calcium lactate and parathyroid. Marmite, fruit, eggs, arkasa, milk, tomato juice, liverjuice, butter.

The condition did not improve, and on May 3rd the left cornea ulcerated. The child died on May 6th, three weeks after admission.

The photograph (Fig. 5) was taken three days before death.

Case 4.—Female, normal full-time child. When the child was 3 months old the mother became pregnant again and, at term, gave birth to twins. This child was given arkasa and breast milk. She put on weight and grew normally, except for some attacks of intertrigo and sore eyes. At 10 months old she stopped gaining weight and was ordered tinned milk, but was given practically an exclusive diet of arkasa and kenki. She was given cod-liver oil and malt, and quinine and iron when she attended the children's hospital, which was about once in six weeks. This treatment appeared to have delayed the onset of the disease.

At 14 months old she was admitted with the disease apparent. The face, feet and hands were swollen, mouth sore, spleen and liver enlarged. Stools acid, no ova or protozoa; saliva acid to litmus. The blood contained no parasites. Reflexes normal. Purulent discharge from eyes and vagina. Irritable. There was mottling of the skin of the forearms and legs, most marked at the ankles and wrists. The skin was desquamating over these dark areas, leaving light-coloured raw patches underneath. These light-coloured patches take a long time to heal and to become normally pigmented.

Treatment: as in previous cases.

This patient appeared to recover completely while in hospital but after discharge the improvement was not maintained. When last seen at 18 months old she only weighed 15 lb. There was a return of the œdema of the face, photophobia, and irritability.

Fig. 6 shows the child convalescent at the age of 15 months. The wrinkling

FIG. 6.—Case 4, convalescent.

on the dorsum of the feet can be seen, where the œdema is disappearing; also the dark mottling on the legs and the light coloured areas, where the new skin is showing, but has not yet become pigmented.

Case 5.—Female. The mother had had four other children. She said they had all died at about 2 years old of the same condition. She said she never had much milk, and in the present case it dried up when the child was less than a year old. She brought the child regularly to the hospital, and was given instructions about the diet, which she said were carried out. Although the child was obviously not doing well, she refused to have it admitted. Cod-liver oil and malt was prescribed, and it appears that this postponed the appearance of the skin lesions. When the child was about 2 years old the mother went away to the country. They returned after two months. The child showed every sign of the disease in its most profound form. After the

child's death, the mother came one day and confessed that she had not fed her on anything but 'garri,' a Nigerian food made of cassava, arkasa and kenki. She had only once given the child any milk, and never again, as it made the child's mouth 'putto-putto' or messy.

Differential diagnosis.—The disease described above shows differences from other conditions with which it may be compared.

In pink disease œdema, wasting and irritability occur as in the present disease; but the skin lesions are quite different and the deep reflexes are lost in pink disease.

FIG. 7.

Pellagra is generally described in adults, and the character and distribution of the skin lesions are not like those described above. Similarities between the two diseases are seen in the insidious onset, wasting, mental changes, diarrhœa, and the history of a diet of maize.

In beri-beri anasarca, pericardial effusion and nervous symptoms are prominent. Skin lesions are not essential.

In pemphigus the eruption is bullous at some stage.

Treatment.—The similarity which this disease bears towards other deficiency diseases suggested that the remedy should be dietetic. In the

absence of any accurate knowledge as to what the defect was, a full and varied diet, rich in accessory substances, was employed, together with various drugs. In the early cases this appeared to cure, and in some of the advanced cases it appeared to arrest the progress of the disease.

It has been impossible to conduct a scientific investigation into the cause, or to make any controlled experiments into the nature of the cure. But my general impression is that the most important elements in the treatment adopted were cod-liver oil and a good brand of tinned milk. Nestlé's sweetened condensed milk seemed to answer the purpose. The cod-liver oil given to out-patients seemed to delay the onset of the fulminating stage; but it was only with in-patients, for whom an adequate supply of good milk could be assured, that a cure was established.

In three of the most recent cases attending hospital the disease was first seen in an early stage. Œdema of the hands and feet was noticed, and a history of a defective diet was then elicited. In two cases the mother was pregnant, and in the third the mother had died in child-birth. Each of these children was admitted to hospital. They were given a full varied diet containing a good brand of tinned milk, eggs, marmite, fruit, cod-liver oil and malt. The œdema subsided, the irritability grew less, but the typical skin condition began to develop on the ankles. This, however, did not become serious nor did it last for long, and the general condition of the child improved rapidly. The weight increased, and in each case the child was sent out of the hospital apparently cured.

Prevention.—The young children on the Gold Coast suffer gravely from the lack of a proper diet and from the ignorance of their relations. The authorities might well actively encourage the use of milk. Merchants should be able to import reputable brands of milk, duty free if possible. The agriculturists will bestow an inestimable blessing when they will introduce a milking strain of goats to cross with the native goats. The educationalists might well devote time to teaching their pupils how to obtain milk, butter, and cheese from these animals, and include information on hygiene and feeding in the educational syllabus.

Discussion.—There are several ætiological factors which may possibly play a part in the production of this syndrome.

Breast milk is probably deficient in some factors, which are at present uncertain.

As maize was the only source of the supplementary food, some amino-acid or protein deficiency cannot be excluded as a cause.

As regards vitamin deficiency there is no evidence pointing to lack of vitamins A, C, D or E. That there is a deficiency of some part of vitamin B complex cannot be excluded, although the disease described here does not resemble either pellagra or beri-beri.

Summary.

A description is given of a disease occurring in the Gold Coast Colony in children of either sex between the ages of one and four years. The disease appears to take from four to twelve months to declare itself. There is a history of deficient breast-feeding, and the only supplementary food used is a preparation of maize.

The lesions of the skin are extensive, well-marked and characteristic. They may be accompanied by slight œdema of the extremities. The mucous membranes are often inflamed and ulcerated, and the saliva frequently acid. In the late stages corneal ulcers are often present. The nervous system shows persistent irritability, but the reflexes are normal.

The temperature is irregular and the pulse is rapid. There is no great anæmia, and the blood shows no leucocytosis. The Wassermann reaction is negative, and no parasites are to be found in the blood except where there is associated malaria.

There is a tendency to vomiting, and in chronic cases wasting may be severe. Diarrhœa occurs and becomes persistent in the later stages. The stools show undigested food, but no ova or parasites. The liver and spleen may be enlarged.

The respiratory system is not necessarily affected. The urine may show a trace of albumin.

Post mortem nothing characteristic is found except a very fatty, almost diffluent, liver. There may be some degeneration of the kidneys.

The treatment consists in the administration of an adequate diet rich in accessory substances.

I have to thank the staff of the Research Institute at Korle Bu for the pathological findings, Mr. Buckner for the photographs and the Hon. Director of Medical and Health Services for permission to publish these observations. I am indebted to Dr. H. M. M. Mackay and others for their help and criticism. Finally, the absence of any quotations from the literature, for which I tender apologies, is due to the fact that I am out of reach of reference libraries.